SYNTHETIC GENOMICS | *Options for Governance*

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Executive Summary

Gene and genome synthesis, that is, constructing long stretches of DNA from constituent chemicals, provides scientists with new and unparalleled capabilities both for understanding biology and for using it for beneficial purposes. But along with new capabilities come new risks.

Synthetic genomics combines methods for the chemical synthesis of DNA with computational techniques for its design, allowing scientists to construct genetic material that would be impossible or impractical using more conventional biotechnological approaches. The constructed DNA can then be used in a wide variety of applications that could potentially lead to improvements in human health, the environment, and basic research, among others.

The synthesis of relatively short stretches of DNA (called oligonucleotides) using specialized machines has been possible for nearly 25 years. Two advances have changed the landscape in the last five years or so. First, researchers have learned to speed up the process of stitching together small pieces of DNA into large, gene- or genome-sized pieces, so that the DNA of, for example, a medium-sized virus can be constructed in a matter of weeks. Second, there has been a proliferation of companies with proprietary technologies that are able to synthesize gene- and genome-length DNA at prices that are within reach of many researchers; these prices are rapidly dropping.

While at least some of these DNA sequences could be engineered in the laboratory using various recombinant DNA technologies, the efficiency with which arbitrary sequences of DNA can be synthesized vastly improves the speed and ease of conducting experiments and developing applications that were previously extremely difficult, or simply not possible. The ability to quickly construct or purchase whole genes and genomes has the potential to accelerate research in a variety of areas, from high-value pharmaceuticals to biofuels to power our cars; this capability may also make it possible to respond quickly to emerging threats, such as by developing and manufacturing vaccines during a pandemic. Improvements in the speed and cost of DNA synthesis are also opening the field to new participants (e.g., engineers seeking new tools) that may transform biotechnology.

However, as in the case of many technologies, synthetic genomics may be "dual-use:" in addition to useful advances for society, it may provide those with nefarious intent new ways to harm. Although dual-use concerns exist for almost all technologies, the power and accessibility of modern biotechnology—with synthetic genomics being a prime example—makes these concerns particularly salient. Examination of the risks and benefits of this technology today has become entwined with the events of September 11, 2001 and the subsequent anthrax attacks.

This report is the result of a 20-month examination, funded by the Alfred P. Sloan Foundation, of the safety and security concerns posed by this new technology. With a core group of 14 additional people with a wide range of expertise, we undertook three tasks: assess the current state of the technology, identify potential risks and benefits to society, and formulate options for its governance.

We found no "magic bullets" for assuring that synthetic genomics is used only for constructive, positive applications. We did, however construct a series of policy interventions that could each incrementally reduce the risks from this emerging technology and, if implemented as a coordinated portfolio, could significantly reduce the risks.

We defined three major points for policy intervention:

- Commercial firms that sell synthetic DNA (oligonucleotides, genes, or genomes) to users.
- Owners of laboratory "bench-top" DNA synthesizers, with which users can produce their own DNA.
- The users (consumers) of synthetic DNA themselves and the institutions that support and oversee their work.

For each intervention point, we formulated a series of policy options. Each option was evaluated for its ability to reduce biosecurity and biosafety risks, the burden of implementation (in both resources and opportunity costs), and the degree of additional research that would be required for an option to be useful. We presented our preliminary options and analyses before a large group of subject matter experts and other stakeholders and solicited feedback that we used to revise and refine the options which are presented in their final form in this report.

The first set of options applies to firms that supply synthetic DNA, both those that supply gene-and genome-length strands of DNA and those that supply much shorter oligonucleotides. These options, treated in the report in parallel for gene-supplying firms and oligonucleotide-supplying firms are:

I-1. Require commercial firms to use approved software for screening orders.

I-2. People who order synthetic DNA from commercial firms must be verified as legitimate users by an Institutional Biosafety Officer or similar "responsible official."

I-3. Require commercial firms to use approved screening software ***and*** to ensure that people who place orders are verified as legitimate users by a Biosafety Officer.

I-4. Require commercial firms to store information about customers and their orders.

The second set of options is aimed at the oversight or regulation of DNA synthesizers and the reagents used in DNA synthesis.

II-1. Owners of DNA synthesizers must register their machines.

II-2. Owners of DNA synthesizers must be licensed.

II-3. A license is required to both own DNA synthesizers ***and*** to buy reagents and services.

Unlike the first two sets of options, which anticipate and are intended to help forestall the possibility that synthetic genomics may be misapplied by those with malicious intent, the final set of options is aimed exclusively at the legitimate users of the technology. These options cover both the education of potential users of synthetic DNA and the prior review of experiments that scientists and engineers might want to conduct:

III-1. Incorporate education about risks and best practices as part of university curricula.

III-2. Compile a manual for "biosafety in synthetic biology laboratories."

III-3. Establish a clearinghouse for best practices.

III-4. Broaden Institutional Biosafety Committee(IBC) review responsibilities to consider risky experiments.

III-5. Broaden IBC review responsibilities, *plus* add oversight from a national advisory group to evaluate risky experiments.

III-6. Broaden IBC review responsibilities, *plus* enhance enforcement of compliance with biosafety guidelines.

The report presents no recommendations. A summary table of our evaluation of the various options is presented below. The options are detailed in the text of this report. To help decisionmakers choose a preferred set of options, we also include several illustrative portfolios, ranging from a modest set of controls to one that is quite aggressive. When choosing a portfolio, each policy maker will draw on his or her own values, priorities, prior beliefs, and extent of risk aversion to security and safety threats. We believe that any of the options that we include, alone or more usefully in combination, can provide a meaningful response to the threat posed by this otherwise extremely promising technology.

Summary Table of Options

Does the Option:	Gene Firms				Oligo Manufacturers				DNA Synthesizers			Users and Organizations					
	IA-1. Gene firms must screen orders	IA-2. Biosafety officers must certify people who place orders	IA-3. Hybrid: Firms must screen and biosafety officer must verify people	IA-4. Firms must store information about orders	IB-1. Oligonucleotide manufacturers must screen orders	IB-2. Biosafety officer must verify people who place orders	IB-3. Hybrid: Firms must screen and biosafety officer must verify people	IB-4. Firms must store information about orders	II-1. Owners of DNA synthesizers must register their machines	II-2. Owners of DNA synthesizers must be licensed	II-3. Licensing of equipment, plus license required to buy reagents and services	III-1. Education about risks and best practices in university curricula	III-2. Compile a manual for 'Biosafety in Synthetic Biology' Laboratories	III-3. Establish a clearinghouse for best practices	III-4. Broaden IBC review responsibilities	III-5. Broaden IBC review, plus oversight by National Advisory	III-6. Broaden IBC review, plus enhanced enforcement
Enhance Biosecurity																	
by preventing incidents?	◉	○	●	○	○	○	◉	○	○	○	○	○	–	–	○	○	○
by helping to respond?	–	–	–	○	–	–	–	○	○	○	○	○	–	–	–	–	–
Foster Laboratory Safety																	
by preventing incidents?	○	–	○	–	○	–	○	–	–	–	–	◉	●	○	○	◉	◉
by helping to respond?	–	–	–	–	–	–	–	–	–	–	–	◉	–	–	–	○	–
Protect the Environment																	
by preventing incidents?	○	–	○	–	–	–	–	–	–	–	–	◉	●	○	○	◉	◉
by helping to respond?	–	–	–	○	–	–	–	○	–	–	–	○	◉	◉	○	–	–
Other Considerations:																	
Minimize costs and burdens to government and industry?	◉	◉	○	●	○	◉	○	●	●	◉	◉	◉	○	◉	◉	◉	○
Perform to potential without additional research?	◉	●	◉	◉	○	●	◉	◉	●	●	◉	◉	○	○	◉	◉	◉
Not impede research?	◉	◉	◉	●	○	○	○	●	◉	◉	○	●	◉	●	◉	◉	○
Promote constructive applications?	–	–	–	–	–	–	–	–	–	–	–	●	○	◉	○	–	–

Key to Scoring:

- ● Most effective for this goal. Most effective performance on this consideration.
- ◉ Relatively effective.
- ◉ Moderately effective.
- ○ Somewhat effective.
- ○ Minimally effective.
- — Not relevant.

Reading the evaluation diagrams

These diagrams found throughout the report allow for easy comparisons within and between options regarding their effectiveness in achieving the policy goals of biosecurity and biosafety, and their performance on other considerations.

Reading down the columns allows for an evaluation of the performance of a particular option on one goal relative to the other goals. Reading across the rows allows for comparison of the effectiveness of each option with respect to the others on any given goal or consideration. Those that perform better are indicated with circles that have more dark fill; those that perform worse have less fill.

These levels are qualitative: they only indicate that one option performs better or worse than another, but not by how much.

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Introduction

Synthetic genomics combines methods for the chemical synthesis of DNA with computational techniques to design it. These methods allow scientists to construct genetic material that would be impossible or impractical to produce using more conventional biotechnological approaches.

For instance, synthetic genomics could be used to introduce a cumulative series of changes that dramatically alter an organism's function, or to construct very long strands of genetic material that could serve as the entire genome of a virus or, some time in the near future, even of more complex organisms such as bacteria.

Scientists have been improving their ability to manipulate DNA for decades. There is no clear and unambiguous threshold between synthetic genomics and more conventional approaches to biotechnology. Chemical synthesis can be used to make incremental changes in an organism's genome, just as non-synthetic techniques can generate an entirely new genome. Nevertheless, the combination of design and construction capabilities gives synthetic genomics the potential for revolutionary advances unmatched by other approaches. Synthetic genomics allows scientists and engineers to focus on their goals without getting bogged down in the underlying molecular manipulations. As a result, the breadth and diversity of the user community has increased, and the range of possible experiments, applications, and outcomes has been substantially enlarged.

Such revolutionary advances have the potential to bring significant benefits to individuals and society. At the same time, the power of these technologies raises questions about the risks from their intentional or accidental misuse for harm. Synthetic genomics thus is a quintessential "dual-use" technology—a technology with broad and varied beneficial applications, but one that could also be turned to nefarious, destructive use.[1,2] Such technologies have been around ever since the first humans picked up rocks or sharpened sticks. But biology brings some unique dimensions: given the self-propagating nature of biological organisms and the relative accessibility of powerful biotechnologies, the means to produce a "worst case" are more readily attainable than for many other technologies.[3]

The four authors embarked on this study of synthetic genomics to assess the current state of the technology, identify potential risks and benefits to society, and formulate options for governance of the technology. Assisted by a core group of 14 additional people with a wide range of expertise, we held three expert workshops and a large invitational meeting with a diverse set of decision-makers, subject-matter experts, and other important stakeholders. We obtained additional information by commissioning papers from experts on various topics. An overview of the information elicited from these activities and a detailed description of the policy options for governance are contained in this report.

The goal of the project was to identify and analyze policy, technical, and other measures to minimize safety and security concerns about synthetic genomics without adversely affecting its potential to realize the benefits it appears capable of producing. We hope that this study will contribute to a wider societal discussion about the uses of the technology.

Introduction to Synthesis

Researchers have had the basic knowledge and tools to carry out the ***de novo*** synthesis of gene-length DNA from nucleotide precursors for over 35 years.[4] At first, however, these "from scratch" synthesis techniques were extremely difficult, and constructing a gene[i] of just over 100 nucleotides[ii] in length could take years. Today, using machines called DNA synthesizers, the individual subunit bases adenine (A), cytosine (C), guanine (G), and thymine (T) can be assembled to form the genetic material DNA in any specified sequence, in lengths of tens of thousands of nucleotide base-pairs[iii] using readily accessible reagents.[iv]

Precisely how a scientist or engineer will obtain the pieces of DNA of interest will vary depending on the resources and preferences of that individual (Figure 1). The most straightforward way to obtain a gene- or genome-length stretch of DNA is to order it from a ***commercial gene synthesis company***. There are at least 24 firms in the United States and at least an additional 21 firms worldwide that provide this service (Table 1). Many of these firms use proprietary technologies to produce extremely long pieces of DNA; the longest strand reported to date is 52,000 base pairs, synthesized by Blue Heron Biotechnology of Bothell, Washington.[5] Currently, many types of technologies used by firms are proprietary and are not available for purchase by individual users. (See Figure 1, Panel A).

Alternatively, a scientist may wish to assemble gene- or genome-length DNA on his or her own starting from smaller pieces of DNA called oligonucleotides or oligos. Oligos are sub-gene length stretches, typically from about 15 base-pairs to about 100 base-pairs long. The smaller oligos can be used in laboratories in diagnostic assays and other standard laboratory protocols. The longer oligos, though, from about 40 base-pairs on, can actually be used to construct gene- and genome length DNA (Figure 2).

Country	Number of Gene Synthesis Companies (minimum)
United States	24
Germany	5
Canada	4
China	2
France	2
Russia	2
Australia	1
Netherlands	1
Norway	1
South Africa	1
Switzerland	1
United Kingdom	1

Table 1: Estimate of number of DNA synthesis companies worldwide capable of supplying gene- and genome-length products[v].

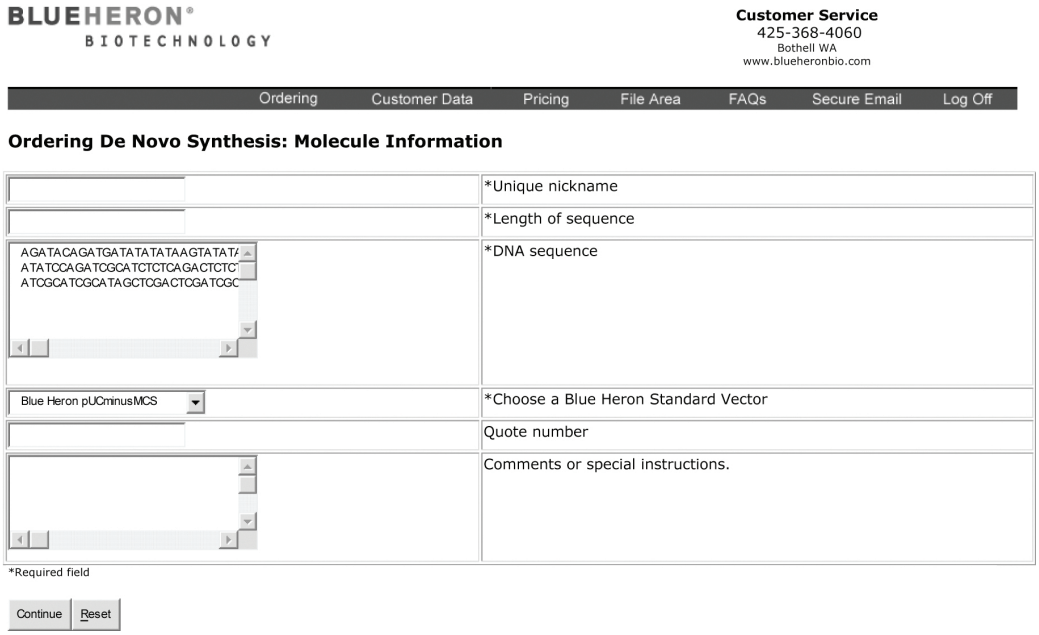
Synthetic genomics is a quintessential "dual-use" technology—a technology with broad and varied beneficial applications, but one that could also be turned to nefarious, destructive use.

[i] Genes range in length from typically hundreds to a few thousand nucleotides long; they can, however, vary widely, and the full definition of what constitutes a gene may include sequences as small as the tens and into the tens of thousands of nucleotides.

[ii] A nucleotide is a basic unit of nucleic acids; it consists of several chemical groups including its defining base and may be ribonucleic or deoxyribonucleic acid (RNA and DNA respectively)

[iii] A base-pair is the combination that occurs in a double helix of DNA: A pairs with T; G pairs with C. In describing length, "bases" and "base pairs" are frequently used interchangeably.

[iv] "Reagents" is an inclusive term describing many of the chemicals and related substances used in laboratory processes.



Panel A

Panel B

Figure 1: Mail order or make it yourself. The basis of gene- and genome synthesis is the machines that produce polynucleotides for subsequent manipulation.

Panel A: Commercial genes or oligos. Firms throughout the world use synthesis technologies (in many cases proprietary) to make completed, characterized gene- or genome-length DNA for customers. In this example, customers simply enter the desired sequence through a screen interface; about 6-8 weeks later the DNA is delivered. (Credit: Blue Heron Biotechnology)

Panel B: A laboratory-benchtop oligonucleotide synthesizer. Individual laboratories can buy oligonucleotide synthesizers to generate oligos that can then be manipulated to make a full-length gene or genome. These synthesizers are available commercially from manufacturers such as Applied Biosystems, or may be purchased secondhand on auction sites such as LabX and eBay. These are similar in function to machines used by commercial oligonucleotide synthesis companies.

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[v] These numbers represent minimums based on our ability to confirm that companies referencing gene- or genome synthesis are in fact capable of doing so. There almost certainly are additional companies involved in synthesizing genomes but we could not independently identify and confirm these.

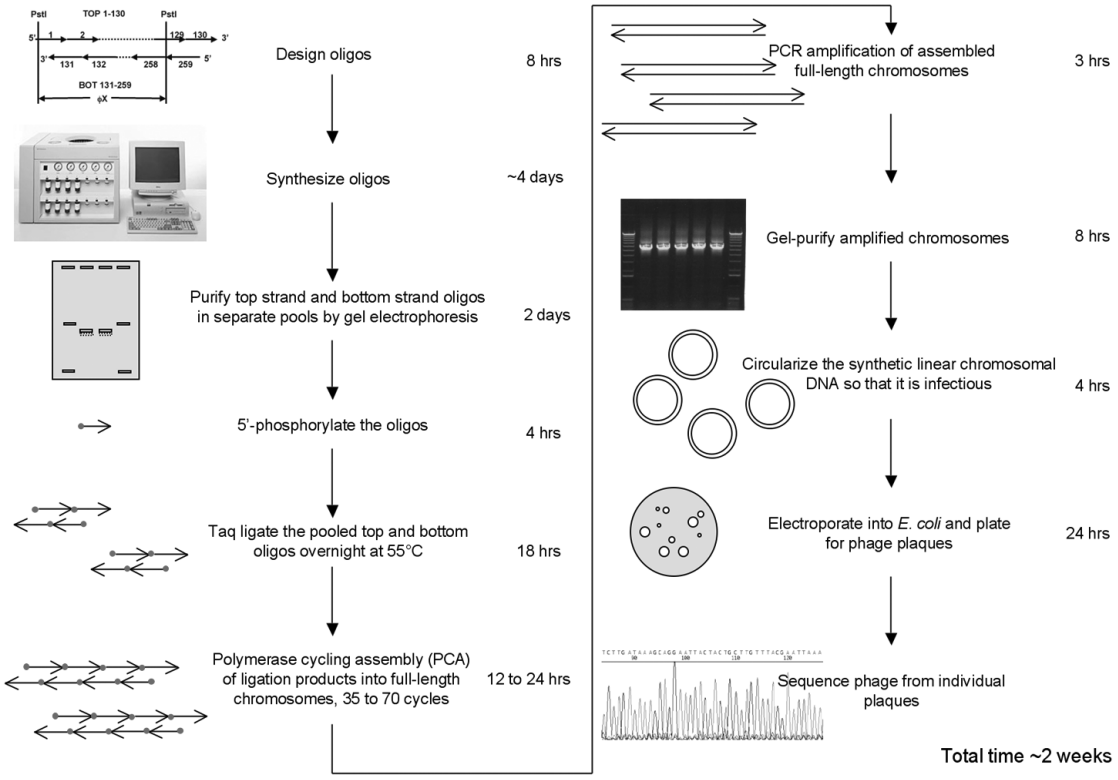

Figure 2: Gene- and genome-length DNA construction using oligonucleotides. Oligonucleotides may be purchased or synthesized in a laboratory. They are then subjected to a series of biochemical manipulations that allows them to be assembled into the gene or genome of interest. This example illustrates the construction of the bacteriophage phiX174 (approximately 5500 nucleotides) in about 2 weeks. (Smith et al. 2003 *PNAS 100:* 15440. Copyright National Academy of Sciences).

Oligos can either be ordered from a ***commercial oligonucleotide manufacturer***, or they can be made easily within a laboratory using a specialized machine for that purpose. It is unclear exactly how many firms commercially produce oligos.[vi] Oligos are so important to modern biology that many universities and firms had established central production facilities to produce them for in-house use. At present, however, economies of scale permit commercial firms to make them less expensively, and frequently more quickly, than these facilities. Many universities are letting their synthesizers lay idle, or are even re-selling or trading them in for other equipment.[vii] The research community in the United States is therefore heavily dependent on commercial suppliers for oligo production.

However, even the most versatile firms may not completely meet the needs of specific users; thus, some scientists prefer to make oligos in their own laboratories. This can be done on a commercially available oligo synthesizer, a

[vi] Based on a variety of Web searches and discussions with participants at our workshops, it seems reasonable to estimate a minimum of 25 companies in the United States alone that have major efforts in oligonucleotide production; there are probably many more that are capable of making oligonucleotides but for which this is not a major part of their business, or that do not have a Web presence and thus were overlooked in our searches.

relatively inexpensive, standard piece of equipment that fits easily on a laboratory benchtop. (Figure 1, Panel B)

Regardless of the technique used to construct a gene or genome, DNA synthesis technologies offer a much more efficient way to do many of the same things that can be done with standard recombinant DNA or other biochemical or molecular biology techniques. However, the efficiency of modern synthetic DNA technologies together with improved design capabilities offers the potential for revolutionary advances. Synthetic genomics may lead to qualitatively new capabilities, broadening the number of users of biotechnology, and enabling complex applications to be developed by separating higher-level design concepts from the underlying molecular manipulations.

Early Milestones

The first complete chemical synthesis of a gene was described in the early 1970s by Har Gobind Khorana and his colleagues. It was an arduous task, taking Khorana and 17 co-workers years to assemble a very small gene (207 base-pairs).[6, 7] Scientists had been "reading" the genetic code for years. Khorana and colleagues were the first to accomplish the next step: "writing" the code of the building blocks of life by making a small but functional gene.

In the decades following Khorana's achievement, scientists searched for an efficient chemical means to synthesize genes. Many groups published articles describing a wide variety of approaches to the synthesis of long stretches of DNA.[8, 9] By the mid-1990s, Willem Stemmer and co-workers were able to synthesize a large gene and vector system (approximately 2700 base-pairs) using a variation of a standard molecular biology laboratory tool, the polymerase chain reaction. In a straightforward fashion, on the order of days, any gene could be mutated at any number of locations in the sequence and tested for any given property. This technique had implications for everything from the study of evolution to the discovery and testing of new drugs.[10]

Other groups of researchers were exploring the problems involved in the synthesis of gene-length pieces of DNA via their work with viruses, which can serve as model systems for a variety of biological inquiries and are important in their own right. In 1981, Vincent Racaniello and David Baltimore described the construction of an infectious poliovirus by the joining of cDNA clones.[viii];[11, 12] In 1999 an influenza virus type A was generated entirely from cloned DNA virus segments.[13] (Earlier, others had made infectious virus from cDNA clones, but those systems required helper viruses.[14])

In all of these synthesis experiments, the goals of the researchers were both scientific and applied: to understand the natural world more completely, and to apply that knowledge toward beneficial applications. The potential for misusing these techniques for bioterrorism was acknowledged, but prior to the attacks of September 11, 2001, these discussions occurred more among professionals concerned specifically about biowarfare and bioterrorism than among members of the biological research community or the public.

In 2002, a team of researchers at the State University of New York led by Eckard Wimmer reported the assembly of an infectious poliovirus constructed in the laboratory directly from nucleic acids.[15] Although this work was built on the prior examples of synthesis noted above, Wimmer's work demonstrated for the

Prior to the attacks of September 11,2001, biosecurity discussions occurred more among professionals concerned specifically about bioterrorism than among members of the research community.

[vii] Discussion at 26-27 September 2005 Workshop: Technologies for Synthetic Genomics.

[viii] cDNA ("complementary" or "copy" DNA) clones are pieces of DNA isolated from a source such as cells; they are processed so that they can be used easily in the laboratory. For example, they are usually inserted into a piece of carrier DNA called a vector that allows for the easy amplification of the piece of DNA of interest.

first time in a post-September 11 world the feasibility of synthesizing a complete microorganism—in this case, a human pathogen—using only published DNA sequence information and mail-ordered raw materials.

The next year, a group from the Venter Institute (formerly the Institute for Biological Energy Alternatives) published a description of a similar technique applied to the construction of phiX174 (a virus that infects bacteria, called a bacteriophage).[16] The advance here was not so much in length of the DNA strand, as this virus is somewhat smaller than poliovirus, but in efficiency: compared to the one year or so required to synthesize and validate infectious poliovirus, a precise copy of a fully-functional phiX174 was synthesized in approximately 2 weeks. Although both poliovirus and phiX174 are relatively small viruses, approximately 7400 and 5400 nucleotides respectively, the lessons learned from these synthesis experiments are directly applicable to learning how to construct larger and more complex genomes.

More recently, DNA synthesis techniques have been applied to constructing viruses that could not otherwise be easily obtained in nature or from laboratory collections. The genome of the influenza virus strain responsible for the 1918 influenza pandemic was constructed from scratch, using only the sequence data available from analyses of DNA from frozen or paraffin-fixed cells recovered from epidemic victims.[17] Late in 2006, a viral "fossil" of a human endogenous retrovirus—a viral genome that had been incorporated directly into the human genome at some earlier point in human evolution, in this case, around 5 million years ago—was resurrected using a variety of synthetic techniques,[18] further illustrating the feasibility of reconstructing extinct viruses.

Additional dramatic increases in the speed and accuracy of DNA synthesis would be necessary to permit realization of an important goal for many in the synthetic biology community: the synthesis not just of viruses but of whole bacteria, which have much larger genomes. Today, a number of groups are working to design and construct from scratch bacterial genomes as well as simple chromosomes of eukaryotic cells (those containing a cell nucleus), such as yeast.[19]

Designing ways to impede malicious uses of the technology, while at the same time not impeding, beneficial ones poses a number of policy challenges.

Implications of the Technology

"Since the sequence is generated by chemical synthesis, there is full choice in the subsequent manipulation of the sequence information. This ability is the essence of the chemical approach to the study of biological specificity in DNA and RNA," Khorana observed in 1979.[20] Today, the rapidly-advancing technology of synthetic genomics embodies this powerful approach. Whereas other recombinant DNA methods start with an organism's genome and modify it in various ways, with results that are constrained by the original template, synthetic genomics permits the construction of any specified DNA sequence, enabling the synthesis of genes or entire genomes.

This capability provides a new and powerful tool for biotechnology, whose most far-reaching benefits may not yet even be envisioned. But along with such power comes the potential for harm. Given this inherent dual-use risk, designing ways to impede malicious uses of the technology, while at the same time *not* impeding, or even promoting, beneficial ones poses a number of policy challenges for all who wish to use, improve, or benefit from synthetic genomics.

Further, the ability to carry out DNA synthesis is no longer confined to an elite group of scientists as was the case for the first several decades of research using recombinant DNA. Now, anyone with a laptop computer can access public DNA sequence databases via the Internet, access free DNA design software, and place an order for synthesized DNA for delivery.

In addition, synthetic genomics raises new safety issues for those who would be most immediately affected by this research: laboratory

staff as well as the community and the environment surrounding the laboratories. Many of these safety issues were considered three decades ago at the meeting on recombinant DNA at the Asilomar Conference Center in Pacific Grove, California, which established the foundation of biosafety as it is practiced in the United States today.

Interestingly, at the beginning of the Asilomar meeting it was decided not to consider biological warfare issues, even though the organizers were apparently cognizant of these concerns at the time and were even prodded a bit about them. According to a contemporaneous report on the meeting, "[T]here seems enough hazard already in pure and simple carelessness, and at the outset of the conference it has been agreed that the issue of new horizons in biologic warfare will not even be raised; for the moment, it is first things first."[21]

The major biosafety issue discussed at Asilomar—the safety of transmitting genes from one organism to another organism via a third organism (a vector such as a virus or bacterium)—has echoes in concerns expressed for synthetic genomics today: how to assess the safety of chimeric organisms; i.e., those that have genomes derived from a very large number of initial sources. Specifically, using standard recombinant DNA cut-and-paste techniques, it is possible to readily assemble a chimera from tens of sources, but synthetic constructions could be from hundreds of sources or more. How to evaluate such constructions for biological safety concerns remains murky.[22]

While few data suggest that such higher-order chimeras will be dangerous just so, this concern has nonetheless prompted some to suggest that all synthetic genomics protocols should take place under levels of biological containment used for the most dangerous human and agricultural pathogens (i.e. Biological Safety Level -3 or -4).[23] Requiring such containment would have the effect of making such work quite expensive, and would thus restrict it to far fewer labs than might utilize it otherwise.

A policy framework to address the development and use of synthetic genomes for contained use must precede any analysis of the intentional release of engineered microorganisms into the environment; thus we have focused on the former. As with several other general concerns about biotechnology and genetic modification, the intentional release of genetically modified microorganisms into the environment is still quite controversial. All such uses are regulated by the Environmental Protection Agency under the Toxic Substances Control Act.[24]

We follow several earlier studies that have looked at societal issues related to synthetic genomics and synthetic biology and that have made policy proposals or recommendations. Among the earliest was a study examining the bioethics of synthesizing a bacterium[25], following a proposal to use synthetic genomics to construct a minimal bacterial genome.[26] Several National Research Council committees have reported on a number of biological security issues.[27, 28, 29] The best-known of these, commonly called the Fink Committee Report, was the basis for the establishment of the National Science Advisory Board for Biosecurity (NSABB).[30] The NSABB has already released a report on biosecurity concerns related to the synthesis of select agents,[31] and an NSABB working group has developed draft guidance and tools for the responsible communication of dual-use research, including institutional review issues.[32]

In 2004, immediately following the first international Synthetic Biology meeting (SB 1.0) George Church put forth a proposal for the oversight and regulation of DNA synthesizers, and for screening for select agent sequences in DNA orders.[33] Later that year, the Biological and Environmental Research Advisory Committee of the Department of Energy published its own report on the need for action to ensure responsible and thoughtful pursuits in synthetic biology.[34] Voluntary community-based approaches for security and safety are discussed in detail in a white paper by Stephen

A policy framework to address the use of synthetic genomes for contained use must precede any analysis of the intentional release of engineered microorganisms into the environment.

Maurer and others at the University of California, Berkeley.[35]

Other groups and individuals have made specific proposals as well. The ETC Group published an introduction to synthetic biology that discussed a number of concerns regarding the technology and calling for a ban on the intentional environmental release of synthetic organisms "lacking a clear pedigree"[36]. Participants at the international Synthetic Biology 2.0 conference issued a statement calling for the scientific community to take steps to mitigate security concerns related to synthetic biology, such as promoting technologies to ensure that orders for DNA sequences do not contribute to the illicit production of dangerous pathogens.[37] The International Consortium for Polynucleotide Synthesis, an industry group of commercial DNA synthesis firms, has described a potential framework for the screening of orders.[38]

This study focuses on three key societal issues: bioterrorism, worker safety, and protection of communities and the environment in the vicinity of research laboratories.

The societal concerns about this type of emerging technology are broad in scope and include cultural and ethical concerns about manipulating life, economic implications for developed and developing regions, issues related to ownership and intellectual property, concerns about environmental degradation and potential military uses, and so on. Each of these issues deserves thorough consideration. As mentioned above, at the time of the first suggestion of building bacteria from scratch, an ethics study was commissioned and the results were published along with the publication of preliminary data on defining a minimal bacterial genome. The study group found that there was nothing inherent in synthetic genomics research that made it unethical: "The prospect of constructing minimal and new genomes does not violate any fundamental moral precepts or boundaries...."[39]

Nevertheless, the authors noted that: "…[constructing minimal and new genomes] does raise questions that are essential to consider before the technology advances further." Indeed, over the past eight years, and particularly since the events of September 11, other overlapping ethical and safety concerns have arisen, and many groups and individuals have expressed worries about the conduct of synthetic genomics research with respect to a broad array of societal issues. The Rathenau Institute, for example, has issued a report raising a wide array of societal and research community issues that warrant more rigorous analytical attention, including the ethics of constructing new synthetic organisms.[40]

Finally, state-sponsored creation of biological weapons is a concern for all biotechnologies, including synthetic genomics. The Biological and Toxin Weapons Convention (BWC), a treaty with 156 States Parties and another 16 signatories that have not yet ratified it[41] establishes a crucial international norm proscribing the development, acquisition, or production of biological agents as weapons, whether produced by synthetic genomics or any other means. However, the BWC includes no verification and enforcement mechanisms for preventing states from applying synthetic genomics in this way, and many would argue that effective measures for that purpose are not feasible. At any rate, multilateral verification and enforcement are beyond the scope of this paper. Individual nations may also apply diplomatic or military pressure to other nations they believe to be violating norms such as the BWC.

Societal issues addressed in this study

This study focuses on three key societal issues: bioterrorism (for reasons described above), worker safety (a critical part of the scientific enterprise), and protection of communities and the environment in the vicinity of legitimate research laboratories (those most likely to be affected by an accident).

We restricted our purview to synthetic genomics and did not attempt to evaluate or assess broader issues associated with research involving pathogenic microorganisms in particular or biotechnology in general. These latter

issues, including the deliberate environmental release of genetically modified organisms, have been controversial for decades and are beyond the scope of this effort.

Further, we do not deal with state-sponsored research and development programs. No governance measure imposed by a national government will be effective at constraining that government's own activities if the responsible officials within that government choose to evade, ignore, or interpret their way around them. Moreover, no measure taken by researchers, firms, or other non-state entities operating within a government's jurisdiction can necessarily be relied on to resist pressure by that government. In the current international system, the only way to deal with abuses of national governments is through the actions of other governments, either collectively or individually. Such mechanisms are beyond the scope of this study.

Our goal was to develop policy options to address the incremental (novel) risks and benefits presented by synthetic genomics technologies. These policy options, presented in a later section, are organized by actions to be taken and policies to be adopted, rather than in terms of who would implement them. Although some of the options addressed here can be implemented only by government regulation, and others only by community agreement, assigning responsibility is an outcome of the analysis and not an input to it.

We made no assumptions as to whether the options should be voluntary or legally binding (regulatory) in nature and if so, who the regulators should be. By the same token, we do not presuppose that the scientific community will automatically address these issues on its own.

Many have pointed out that the ability to detect, contain, and treat illness that might result from the accidental or intentional release of a harmful synthetic organism can be no better than the ability to respond to naturally occurring outbreaks or to bioterrorism attacks with existing pathogens, which many believe to be inadequate.[42] To remedy this broader vulnerability, a robust public health infrastructure, routine surveillance for unexpected threats, and a flexible, responsive, and adaptive capability for developing, producing, and distributing medical countermeasures (detection, diagnosis, vaccines, drugs, etc.) is critical. Biodefense funding through the National Institutes of Health is addressing some of these needs.[43] The recently created Biomedical Advanced Research and Development Authority (BARDA)[44] will address these needs as well. Improvements in the general ability to detect and respond to public health threats in general will of course apply to any threats from synthetic genomics specifically as well.

Some of the options can be implemented only by government regulation; others only by community agreement. But assigning responsibility is an outcome of the analysis, not an input to it.

Benefits and Risks

Benefits

Recombinant DNA technologies allow individuals to construct novel DNA molecules by joining and modifying fragments of pre-existing genetic material. Today, such work is typically carried out by experts in laboratory settings. The work itself is often ad hoc and laborious. It is not uncommon for skilled researchers to commit months of effort to constructing the genetic material needed just to start a specific experiment.

DNA synthesis allows "decoupling" the design of engineered genetic material from the actual construction of the material.

By contrast, DNA synthesis allows "decoupling" the design of engineered genetic material from the actual construction of the material. DNA can be readily designed in one location and constructed elsewhere. As a result, researchers can devote their time and energy to focusing on the actual challenges of their research (Figure 3). A secondary result of this technological advance is that experiments may be designed to look at wide varieties of sequence variations in experimental settings.

Over the course of the study, we identified several major areas where synthetic genomics could make a unique or significant contribution: as an enabling technology that is changing the nature of basic biological research and as a powerful tool of applied biotechnology with the potential for developing new pharmaceuticals, biological sources of transportation fuels, and manufacturing of other bio-based products.

A recent report[46] from Bio Economic Research Associates estimates that the current global market for DNA synthesis reagents and services is nearly $1 billion, and that the "productivity of DNA synthesis technologies has increased approximately 7,000-fold over the past 15 years, doubling every 14 months. Costs of gene synthesis per base pair have fallen 50-fold, halving every 32 months. At the same time, the accuracy of gene synthesis technologies has improved significantly." The article concludes that "the rapid expansion of these basic technology services will have far-reaching economic impacts as enablers of innovation in many industrial sectors."

Synthetic genomics is even today changing the nature of ***basic molecular biological research***. As an enabling technology, DNA synthesis has already proved to be a significant time saver by shortening the time needed for time-consuming recombinant DNA techniques; in the coming 5 to10 years DNA synthesis will continue to become less expensive as well. Using synthetic genomics to rapidly change the sequence of various genes or whole genomes is becoming a powerful tool for basic research in a number of disciplines. For example, various laboratories are using synthetic genomics to understand the mechanisms of evolution at the molecular level,[47, 48] to define regulators of specific genes or gene pathways and to establish, at the molecular level, the minimal requirements for life.[49]

This capability to make subtle changes at the DNA sequence level may lead to more efficient research and production of ***vaccines for human and animal health*** and related ***diagnostics***. Specifically, the ability to assemble and mutate sequences rapidly could allow for the development of broadly protective vaccines against, and diagnostics for, viruses that themselves are diverse and variable, such as the viral causative agents of severe acute respiratory syndrome (SARS)[50] and hepatitis C.[51]

DNA synthesis techniques have already been applied in research on ***new or improved drugs***. For example, the antimalarial drug artemisinin is naturally produced in the plant *Artemisia annua* through a complex metabolic pathway that cannot feasibly be reconstructed in yeast using conventional biotechnological methods.[52] Purification from the natural plant source is a process that is inefficient, expensive, and can

Figure 3, Panel A: Research protocol without synthetic genomics.[45]

To build section alpha, we first cloned parts 5, 6, 7, 8, 12, 13, 14, 15, 16, 18, 20, 22, and 24 into pSB104. We cloned part 11 into pSB2K3. We cloned each part with its part-specific bracketing restriction sites surrounded by additional BioBrick restriction sites. We used site-directed mutagenesis on parts 6, 7, 14, and 20 to introduce the sites U1, U2, U3, and U4, respectively. Our site-directed mutagenesis of part 20 failed. We used site-directed mutagenesis to remove a single Eco0109I restriction site from the vector pUB119BHB carrying the scaffold Fragment 4. We cloned part 15 into this modified vector. We then cloned scaffold Fragment 4 into pREB and used serial cloning to add the following parts: 7, 8, 12, 13, 14, 16, 18, 20, 22, and 23. We digested the now-populated scaffold Fragment 4 with NheI and BclI and purified the resulting DNA. Next, we cloned parts 5 and 6 into pUB119BHB carrying scaffold Fragment 3. We used the resulting DNA for in vitro assembly of a construct spanning from the left end of T7 to part 7. To do this, we cut wild-type T7 genomic DNA with AseI, isolated the 388 bp left-end fragment, and ligated this DNA to scaffold Fragment 2. We selected the correct ligation product by PCR. We fixed the mutation in part 3 (A1) via a two-step process. First, PCR primers with the corrected sequence for part 3 were used to amplify the two halves of the construct to the left and right ends of part 3. Second, a PCR ligation joined the two constructs. We added scaffold Fragment 3 to the above left-end construct once again by PCR ligation as described above. We repaired the mutation in part 4 (A2, A3, and R0.3) following the same procedure as with part 3. We used a right-end primer containing an MluI site to amplify the entire construct, and used the MluI site to add part 7. We used PCR to select the ligation product, digested the product with NheI, and purified the resulting DNA. We isolated the right arm of a BclI digestion of wild-type T7 genomic DNA and used ligation to add the populated left-end construct and the populated Scaffold Fragment 4. We transfected the three-way ligation product into lJ1127. We purified DNA from liquid culture lysates inoculated from single plaques. We used restriction enzymes to digest the DNA and isolate the correct clones. Next, we added part 11 via three-way ligation and transfection. Because the restriction sites that bracket part 9 (RsrII) also cut wild-type T7 DNA, we needed to use in vitro assembly to add this part to a subsection of section alpha. To do this, we used PCR to amplify the region spanning parts 5–12 from the refactored genome. We cut the PCR product with RsrII and ligated part 9. We used PCR to select the correct ligation product; this PCR reaction also added a SacII site to the fragment. We digested the PCR product with SacI and SacII and cloned onto the otherwise wild-type phage. Lastly, we used the SacII site to clone part 10 onto the phage.

Figure 3, Panel B: Research protocol with synthetic genomics.

FIGURE 3. An immediate application of synthetic genomics. Much time in research and other laboratories is spent manipulating DNA to then conduct experiments. Synthesizing the desired sequence directly saves time and thus allows scientists and engineers to focus on the actual experiments. A second result of this advance is that experiments may be designed to look at wide varieties of sequence variations in experimental settings. Panel A describes a research protocol that took three years of effort. In contrast, ordering the equivalent DNA (Panel B) may take six weeks from order to delivery.

Using synthetic genomics to rapidly change the sequence of various genes or whole genomes is becoming a powerful tool for basic research in a number of disciplines.

contaminate the product with other plant material. Supply depends on the weather and even the political situation in regions where the plant is found. As a first step toward the eventual production of artemisinin in yeast, researchers inserted a synthetic gene for the precursor artemisinic acid into a strain of yeast that had been engineered to produce large amounts of product. The production of artemisinic acid in yeast is currently being optimized for industrial scale-up.

Another research group[53] has described the total synthesis of a 32,000 base-pair gene cluster that codes for polyketide synthase. This DNA synthesis was notable for its length (it remains one of the longest syntheses published to date) and more important that it yielded an active gene product. The enzyme it encodes is in a class of extremely important drugs (including antibiotics, transplant rejection suppressors, and potential anti-cancer drugs). Synthesizing many variants of these genes could provide pools of potential drugs, which could then be screened for the desired properties.[54]

Synthetic genomics could also contribute to the search for ***carbon-neutral energy sources***. A major application of synthetic genomics could be in overcoming biological barriers to cost-effective production of biofuels.[55] Consolidated bioprocessing (CBP) of cellulosic biomass to ethanol is a particularly promising target for this new technology. Scientists are trying to engineer a single organism to include all the multiple steps needed to produce ethanol from cellulose (or at least the fermentable sugars preceding ethanol production).[56] While the use of synthetic genomics to produce all of the enzymes needed for CBP is not the only technique available, it is among the most promising. If successful, CBP might be able to produce ethanol at a cost competitive with gasoline.[57]

Sometimes called "white biotechnology," ***biobased manufacturing*** is becoming a reality. Plants and microbes are being engineered to produce raw materials that can be used to manufacture products that today are typically petroleum-based. The expectation is that biologically based manufacturing will lead to more environmentally friendly products and methods of production. For example, the environmental impacts of plastic manufacturing might be lessened through the judicious use of bioengineering of metabolic pathways using synthetic genomics as one tool.[58, 59]

Finally, millions of new genes are being discovered through metagenomic surveys of microorganisms living in natural environments, looking at thousands of species at the same time. Some of these newly identified genes could be important for ***engineering specific pathways*** into microbes as described above. Because the genes come from microorganisms that typically cannot be cultured in the laboratory, the genes or genomes of interest are known only by their DNA sequence. Synthetic genomics could allow for the reconstruction of these potentially important new genes.

Risks

We looked specifically at three potential risks from the use of synthetic genomics: the risk of its use in bioterrorism, risks to the health of laboratory workers and to the public, and possible harm to the environment from accidental release of microbes with synthetic genomes.

To help us better understand the magnitude of current risks, we commissioned papers from two well-known virologists. We asked them to assess the ease or difficulty of synthesizing a long list of pathogenic viruses, and to compare that to the ease or difficulty of obtaining that virus by other means. We were convinced by their analyses and further discussion at the workshops and the meeting that today, any synthesis of viruses, even very small or relatively simple viruses, remains relatively difficult. In the near future, however, the risk of nefarious use will rise because of the increasing speed and capability of the technology and its widening accessibility. How much the risk will increase remains a matter of debate.

Over the next five years, the key concern is for synthesis of a small number of highly pathogenic viruses that are otherwise difficult to obtain. Ten years from now, it may be easier to synthesize almost any pathogenic virus than to obtain it through other means. Eventually, the synthesis of bacterial pathogens may become possible as well.

In discussions in the workshops and the invitational meeting, we also considered risks from the construction of microbes not currently seen as pathogens of any specific biosecurity concern, and from experiments involving the synthesis of completely novel DNA sequences. While these scenarios may be of concern in the future they are not a major issue today. The policy options that we propose later in this paper are applicable both to today's risks and to those that might emerge over the next decade.

The commissioned papers focus on the impact of synthetic genomics on the production of viruses that could be used as agents of bioterrorism or biological warfare.[60, 61] The papers explore in detail the risks posed by the construction of various classes of viruses.[ix]

The techniques used for synthesizing genomes as discussed above are by no means the only way to construct a viral genome. For several years, laboratories have been synthesizing viral genomes using other techniques. The difference now is that the new techniques provide incremental improvements in cost, speed, and accuracy. Viruses can be constructed using synthetic genomics with varying degrees of difficulty. Sequence data are available for many highly pathogenic viruses, but the quality (accuracy) of these sequences varies. In addition, while the naked nucleic acids of some viruses are infectious on their own (mostly positive-stranded RNA viruses), other viruses require additional molecular components to replicate and hence be infectious.

Even more important, synthesis is by no means the only way a potential bioterrorist might obtain a "threat" virus (a virus that is easily disseminated or transmitted, has a potential public health impact or could cause public panic, or that could cause social or economic disruption). Most viruses can be obtained in nature, although several are hard to find and a few are no longer extant.

Extinct viruses that are also potential threat agents are of greatest concern with respect to the application of synthetic genomics, as there is no other way to obtain them. Variola (smallpox) virus remains of highest concern; the 1918 influenza virus follows closely behind. (In both cases, samples of the viruses exist in a few laboratories, but access to these stocks is tightly controlled).

Of the viruses that are still found in nature, some are easier to find than others. For example, many viruses have reservoirs that are unknown, poorly understood, or only accessible during active outbreaks: the filoviruses such as Marburg and Ebola are among these. Thus, acquiring such viruses would require some luck, good timing, the skill to recognize and isolate the virus of interest, and the ability to transport the virus safely away from the site of an outbreak. Foot-and-mouth disease virus, while endemic in parts of the world, is not found in the United States. While it would be possible for someone to introduce the virus into the United States to precipitate an outbreak, doing so would require a series of steps that might draw attention to a person with malicious intent. A motivated bioterrorist particularly might want to avoid any attention that might come with moving in and out of the country.

Over the next five years constructing an infectious virus will remain more difficult than obtaining it from nature or from laboratory stocks... with a few important exceptions.

[ix] There are several different approaches to categorizing viruses. One is that described by David Baltimore; it classifies viruses according to the strategy they use to generate messenger RNA. Because at least a good part of the ease or difficulty of constructing a virus synthetically hinges on whether synthesized DNA could produce infectious mRNAs on its own, this was for us a particularly useful organizational scheme.

Virus	Type; length of nucleic acid	Select Agent	Where Found	Difficulty of Synthesis
Variola	dsDNA/180kb	Yes	Locked lab	Difficult
1918 influenza	ssRNA, negative stranded; 8 segments ~10kb total	Yes	Locked lab	Moderately difficult
H2N2 influenza (extinct 1968)	ssRNA, negative stranded; 8 segments ~20kb total	No	Laboratories	Moderately difficult
Poliovirus	ssRNA, positive stranded; ~7.7kb	No	Laboratories; in widely in nature Africa and Asia	Easy
Filoviruses (Ebola, Marburg)	ssRNA, negative stranded; ~19kb	Yes	During active outbreaks	Moderately difficult to difficult
Foot-and-mouthss disease virus	RNA, positive stranded; ~9kb	Yes	Certain hoofed animals	Easy
SARS stranded; ~30kb	ssRNA, positive only; others ??	No	2003 strain in labs	Moderately difficult to difficult

Table 2: When is synthesis the preferred route for obtaining viruses? The column labeled "Difficulty of Synthesis" is the consensus of various virologists and molecular biologists who participated in our workshops and meetings. The judgment applies to someone with knowledge of and experience in virology and molecular biology and an equipped lab but not necessarily with advanced experience ("difficulty" includes obtaining the nucleic acid and making the nucleic acid infectious).

For several years, laboratories have been synthesizing viral genomes using other techniques. The difference now is that the new techniques provide incremental improvements in cost, speed, and accuracy.

Viruses are also stored in laboratories as experimental stocks and clinical isolates, and some can be obtained from repositories, such as the American Type Culture Collection (ATCC).[62] Every virus on the Select Agent List[63] is located in a laboratory somewhere. Select agent viruses are subject to oversight and regulation, but other viruses that are not on the list may also be of concern. For example, the coronavirus responsible for the 2003 SARS outbreak is almost certainly extinct in nature. While many labs may have epidemic strains or clinical isolates in their possession, at least in the United States, they are handled under BSL-3 conditions and their distribution is thus at least somewhat monitored. Inquiries about obtaining these viruses from individuals not known to be legitimate researchers should raise suspicions. It is worth noting as well that approximately 8000 patient samples that may harbor the virus likely are stores in hospital freezers throughout the world. To date, there has been no systematic effort track, recover, and centrally preserve and isolate these specimens from the larger community.

A key hurdle for constructing a robustly infectious virus is being able to replicate the correct genomic sequence. This task is not as straightforward as it would initially appear, as viruses that have been maintained in a laboratory setting tend to accumulate mutations; these laboratory strains are the source for many viral sequences currently in databases (the

DNA sequences in databases are continually being updated, however, especially for viruses of scientific and societal interest). Further, merely synthesizing the genome is only one step in a process that requires many steps.

For the purposes of this report, we take as a given that now, or within a few years, any virus with a known sequence can or will be able to be constructed in a relatively straightforward manner. How functional any of these constructed viruses would be is not clear. Several important factors must be kept in mind. For example, the source of a virus is paramount. Viruses found in nature (particularly during an active outbreak) will probably always be the only "sure thing." Constructed viruses (or even viruses somehow obtained from a laboratory) could be as virulent as wild type viruses, but could just as easily be attenuated.

Table 2 contains our best "guesstimate" of the overall difficulty of synthesizing specific viruses. This evaluation is based on several factors: bigger viruses (longer nucleic acid sequences) are harder to synthesize than smaller ones; positive-stranded RNA viruses (in which the nucleic acid is infectious on its own) are easier to construct than negative-stranded RNA viruses, which in turn are easier than DNA viruses. Finally, available sequence data does not always report how virulent the virus supplying that particular sequence was in nature or in the laboratory. Thus, poliovirus is relatively easy to synthesize because it has a small genome made up of positive-stranded RNA and because a large amount of data is available on sequences of known virulence. Variola (smallpox) virus, in contrast, is harder to synthesize because it is a very large DNA virus for which there are fewer data relating infectivity to sequence.

The key conclusion from the papers and discussion at the workshops was that over the next five years constructing an infectious virus will remain more difficult than obtaining it from nature or from laboratory stocks, with a few important exceptions. In ten years, however, the situation might be reversed. For someone hoping to inflict harm, constructing a pathogenic virus might actually be easier than going to the trouble of isolating it from nature or stealing it from a secure laboratory.

Constructing a "designer virus" or "superpathogen" from scratch was seen as a more distant concern, although several examples of unexpected increases in pathogen virulence using recombinant DNA approaches have been published in the literature.[64] Given the current limitations on the understanding of viral pathogenesis and the immune response, using synthetic genomics to increase the pathogenicity of known viruses was considered to be a more probable risk.

Ten years from now, it may be easier to synthesize almost any pathogenic virus than to obtain it through other means.

The Study

The goal of this study was to formulate governance options that will minimize safety and security risks from the use of synthetic genomics, without unduly impeding its development as a technology with great potential for social benefit. We focused on three concerns: bioterrorism, worker safety, and protection of communities and the environment in the vicinity of legitimate research laboratories. We did not attempt to evaluate or assess broader societal issues associated with use of biological weapons in particular or biotechnology in general, for example, we did not consider deliberate release of engineered microorganisms in the open environment. These broader issues have been controversial for decades and are beyond the scope of this analysis.

Our goal in this study was to construct policy options based on the incremental (novel) risks and benefits presented by synthetic genomics technologies. Specifically, these are the risks and benefits beyond those associated with today's widely-used biotechnologies.

The four authors of the report designed and held several workshops to gather and help analyze information. We assembled a core group of 18 people (including ourselves) described in Appendix I; most attended every workshop and were very important in assuring that we identified, researched, and analyzed each policy challenge and option. In addition to the core group, each workshop involved other experts relevant to the workshop topic.

The core group described in Appendix I included a wide variety of perspectives, including synthetic genomics researchers, commercial suppliers of synthesized DNA, policy analysts who focus on bioterrorism, and those who focus on the legal, ethical, and societal implications of biotechnology. The invitational meeting, described below, included an even wider range of participants and perspectives.

Each workshop also included government observers, mostly *ex officio* members of the National Science Advisory Board on Biosecurity. Government officials also attended the invitational meeting.

We held three workshops over 20 months. The first workshop in September 2005 examined ***Synthesis Technologies***. This workshop focused on currently available DNA synthesis technologies and how those technologies might evolve over the next 5 to 10 years. This workshop also identified opportunities for technical interventions to impede the malicious use of the technology. Based on commissioned papers, the attendees examined the materials, equipment, and know-how needed to go from raw materials to phosphoramidite precursors to finished oligonucleotides to full-length genes. The workshop also explored the capabilities of current computer software for screening oligonucleotide and gene-length orders for defined DNA sequences found in pathogens. Focusing mostly on viruses, participants also considered explicitly how the availability of certain kinds of equipment (e.g. DNA synthesizers) and know-how affect how easy or difficult it is to construct a microorganism from raw materials.

The second workshop explored both the applications (benefits) and potential dangers or misuses (risks) of the technology. ***Risks and Benefits Specifically Attributable to Synthetic Genomics***, held in February 2006, explored the question, "How does a world with synthetic genomics differ from a world without it?" With respect to security or safety risks, a key finding of this workshop was that today there are far easier ways to obtain a pathogen than by synthesis, with a few important exceptions. However, within a decade it may be possible to synthesize any virus. Moreover, in many cases it could be easier to synthesize a virus than to find it in nature or to obtain it from a laboratory.

The workshop also explored various aspects of biosafety. A key concern was the number of new researchers coming into the field from non-microbiology backgrounds, and thus lacking experience in handling dangerous pathogens, increasing the risk of laboratory accidents. Issues surrounding the risk assessment of novel genes and genomes (those made as chimeras from many different initial sources) were briefly discussed.

At the final workshop in May of 2006, ***Governance***, we began to evaluate the various policy options that were identified during the first two workshops. We explored the current regulatory mechanisms governing synthetic genomics and evaluated new measures with potential for mitigating risk while preserving benefits.

An invitational meeting was held in December 2006, bringing together, in addition to those who attended the earlier workshops, many governmental agencies, scientists, and, most important, additional stakeholders who were not present at our earlier workshops.

Framing a Policy Response

In the mid-1970s, influential scientists who had pioneered the emerging techniques of genetic engineering called for a moratorium on recombinant DNA research until the safety implications of that work could be more thoroughly reviewed. The 1975 Asilomar Conference marked the initiation of such a review, which has continued on an ongoing basis ever since. Although the initial concerns were clearly appropriate at the time, subsequent experience has shown not only that recombinant DNA research can be performed safely, but that many of the restrictions put into place after the conference were unnecessarily restrictive. On numerous occasions over the subsequent thirty years, restrictions on recombinant DNA research have been relaxed, showing the wisdom of a governance regime that can be readily tailored on the basis of additional experience.

There have been suggestions that synthetic genomics needs "another Asilomar."[65] But Asilomar was an exercise in *self*-governance: the community determined and imposed on itself those procedures needed to ensure safety.[66] Bioterrorists, by definition, are not willing to accept the norms of the research community, and no community can control all subsequent uses of the research results or techniques it develops.

The research community can, however take actions to lessen the risk that scientific and technical advances might be misapplied. Such actions will help maintain confidence among decisionmakers and the public that the continued advance of science and technology will be beneficial to society. Both questions came to the fore after the attacks of September 11, 2001, and the subsequent anthrax letter mailings, which threatened to change the relationship between the security community, the biological sciences, and the public. Moreover, community action and other less formal mechanisms can help to effect an international consensus on some of these issues, probably much faster and more effectively than governmental negotiations or treaties would.

As discussed above, the scientific community has already begun to address what actions it can take on its own to protect the ability of science to advance without contributing to state biological weapons programs or to the actions of rogue bioterrorists. At the same time, the scientific community, law enforcement, and national security officials and others are exploring whether a legally binding regulatory regime is needed to lessen the risk that research materials, expertise, and facilities could be used to make weapons.

A preferred policy solution would ***both*** minimize the risks from nefarious uses ***and*** minimize the impediments to beneficial uses of the technology. Thus, our challenge has been to formulate a series of governance options, recognizing and evaluating the trade-offs between their ability to reduce the safety and security risks from the use of synthetic genomics and the burdens that they would impose on scientists, industry, and the government.

We have also tried to catalyze discussion within the scientific community on the responsible conduct of synthetic genomics research, while at the same time broadening that discussion to include other communities, including the funders, potential regulators, and customers of synthetic biology research and applications.

Our challenge has been to formulate a series of governance options, recognizing the trade-offs between their ability to reduce risks, and the burdens that they would impose.

Policy goals

In the following sections, we present 17 options for the governance of synthetic genomics. These options address three key policy goals:

- ***Enhancing biosecurity***, either by preventing incidents of bioterrorism or by helping law enforcement identify those responsible if incidents should occur.
- ***Fostering laboratory safety***, either by preventing accidents or by helping to respond in the event an accident does occur.
- ***Protecting the environment***, the people and natural ecosystems outside the laboratory.

For each of the 17 options, we have included our judgment about their relative ***effectiveness*** for achieving each of these three goals.

Other evaluation criteria

Of course, the overall ***desirability*** of an option depends on a host of other considerations, as well. Thus, we have evaluated how well each option fares with respect to four other key criteria:

- Does the option hold down ***costs and other burdens to both government and the affected industry***?
- Can the option be implemented today, or is ***additional research required*** before it will be effective?
- Does the option unduly ***impede biological research or progress by the biotechnology industry***?
- Does the option help to ***promote constructive applications*** of the technology?

Policymakers might choose to adopt a framework of adaptive decision making to keep pace with the rapidly changing technology of synthetic genomics.

Additional considerations

Finally, we discuss two additional key considerations:

- Thinking beyond the U.S border to possible ***international implementation.***
- Keeping pace with ***evolving science and technology.***

A general concern for the implementation of every option is whether lack of international implementation would render that option ineffective. Obviously, all of the options would be more effective if adopted by all countries involved in synthetic genomics. However, this fact does not eliminate the value of unilateral implementation; it may just lead to a smaller incremental improvement. Under each of the options we briefly explore the importance of international implementation.

A final consideration is that the science and technology of synthetic genomics is relatively new and is advancing and evolving rapidly. There is no crystal ball with which to predict the future, nor are there policies robust enough to accommodate all plausible futures. To keep pace with such a dynamic situation, policymakers might choose to adopt a framework of "adaptive decision making." Following this approach, policymakers would put in place a suite of options that match today's technologies, the magnitude of today's risks and benefits, and societal priorities. The keys to success are to 1) closely monitor the progress of the science and technology, and 2) be prepared and willing to modify the suite of options accordingly. Not only might tomorrow's choice of options be different, but the array of options from which to choose from might be drastically altered as well.

Policy Options

Identifying intervention points

We identified several promising points for policy intervention by considering the several ways a gene or genome can be synthesized. Specifically we identified four "factors of production" needed to construct genes or genomes: raw materials and reagents, sequence information, equipment, and know-how.

To thwart the intent of a potential bioterrorist, points for policy intervention include:

- At the point of DNA synthesis itself
  - Gene synthesis companies (selling whole genes and genomes)
  - Oligonucleotide manufacturers (selling short stretches of DNA)
  - Laboratory-benchtop DNA synthesizers used in individual laboratories to make short stretches of DNA
  - Raw materials (when linked with the control of DNA synthesizers)

The points for potential intervention to enhance laboratory safety and minimize risks to the environment include:

- The investigator, through such mechanisms as
  - Education
  - Training tools, such as manuals and clearinghouses
- Oversight bodies, such as Institutional Biosafety Committees

The options below address each of these intervention points.

The portfolio of policy options

Below are three groups of policy options relevant to the governance of synthetic genomics. The evaluations are presented both in text and in a summary chart. The chart is helpful for comparing the effectiveness of the various options in enhancing security and safety against other considerations, such as implementation costs. Policy options were evaluated as described above.

The options presented in ***Table 3***, below, are derived from a variety of inputs. In our initial research, we identified a general set of concerns and stakeholders that would be relevant to any discussions of security and safety. Over the course of the three workshops and discussions with the core group and other participants, we developed a deeper understanding of the needs of various actors and how these groups interact with each other. Some of the options were suggested by individuals; others were developed by discussions of the larger group. In all cases, we evaluated each policy option on the criteria (policy goals and other considerations) described in the previous section.

Reading the evaluation diagrams

Five levels of effectiveness (plus "not relevant") were assigned, with circles having more dark fill indicating better performance on a given goal or consideration. These levels are qualitative: they only indicate that one option performs better or worse than another, but not by how much. Comparisons can be made within or between options.

We identified four "factors of production" needed to construct genes or genomes: raw materials and reagents, sequence information, equipment, and know-how.

Table 3: Table of Options

IA. Policies for commercial gene- and genome synthesis firms

1. Require commercial firms to use approved software for screening orders.
2. People who order synthetic DNA from commercial firms must be verified as legitimate users by an Institutional Biosafety Officer or similar "responsible official".
3. Commercial firms are required to use approved screening software *and* to ensure that people who place orders are verified as legitimate users by a Biosafety Officer.
4. Require commercial firms to store information about customers and their orders.

IB. Policies for commercial oligonucleotide synthesis firms

1. Require commercial firms to use approved software for screening orders.
2. People who order synthetic DNA from commercial firms must be verified as legitimate users by an Institutional Biosafety Officer or similar "responsible official".
3. Commercial firms are required to use approved screening software *and* to ensure that people who place orders are verified as legitimate users by a Biosafety Officer.
4. Require commercial firms to store information about customers and their orders.

II. Policies for monitoring or controlling equipment and reagents

1. Owners of DNA synthesizers must register their machines.
2. Owners of DNA synthesizers must be licensed.
3. A license is required to both own DNA synthesizers ***and*** to buy reagents and services.

III. Policies for users and organizations for promoting safety and security in the conduct of synthetic genomics research

1. Incorporate education about risks and best practices as part of university curricula.
2. Compile a manual for "biosafety in synthetic biology laboratories."
3. Establish a clearinghouse for best practices.
4. Broaden Institutional Biosafety Committee (IBC) review responsibilities to consider risky experiments.
5. Broaden IBC review responsibilities *and* add oversight from a national advisory group to evaluate risky experiments.
6. Broaden IBC review responsibilities, *plus* enhance enforcement of compliance with National Institutes of Health biosafety guidelines.

I. Policies for commercial synthesis firms

Description of this intervention point

Today, most researchers who need custom DNA sequences order them from commercial suppliers. Although it is certainly possible to synthesize a gene- or genome-length piece of DNA from its basic building blocks using a DNA synthesizer in one's own laboratory, the work can be accomplished more efficiently and accurately by firms that specialize in this service. A researcher ordering a particular piece of DNA submits the desired sequence electronically over the Internet. The DNA is synthesized in a specialized facility and then shipped to the researcher. By using such firms, researchers obtain more accurate DNA for their experiments, avoid the need for expensive equipment, and minimize the amount of technical expertise needed.

Similarly, the easiest path for a bioterrorist to *synthesize* a pathogen would be to obtain custom-ordered DNA from a commercial firm. For most pathogens at present, however, synthesizing a genome would be more difficult than either stealing it from a laboratory or isolating it in nature. However, as discussed above, for a few viral pathogens that are very difficult to obtain otherwise, synthesis is a plausible alternative.

Today, two types of firms supply synthesized DNA. The first type supplies shorter-length oligonucleotides (single-stranded DNA), typically up to 100 base pairs in length. The bulk of the synthetic DNA (and RNA) market is for such shorter-length pieces, which are used for a variety of purposes. As the first step in synthesizing the 1918 influenza virus, for example, a researcher (or a bioterrorist) might order several hundred oligo-length pieces of DNA that could be assembled to construct the entire 14,600 base pair genome.

A small number of firms—on the order of 50 worldwide, with about half in the United States—specialize in synthesizing gene- and genome-length pieces of double-stranded DNA which are sometimes incorporated into living cells for shipment. Again, using the example of the 1918 influenza virus, the genome consists of eight segments ranging in size from about 900 to 2300 base pairs.[67] A bioterrorist could conceivably order the eight segments and then, with minimal additional manipulation, insert them into an animal cell to form the complete virus.

For a potential bioterrorist, assembling a genome from these larger pieces would be less difficult technically than starting with the shorter-length oligos, and far less time-consuming. Much of the highly skilled labor needed to synthesize a genome is, in essence, readily available for hire in the form of expertise within the synthesis firms. Thus, we believe that options that focus on firms that can synthesize gene and genome-length stretches of DNA and RNA are top priorities for preventing nefarious uses of synthetic genomics.

The difficulty of constructing a genome from commercially synthesized oligos is comparable to the difficulty of starting with oligos constructed in one's own lab with a privately owned DNA synthesizer. However, ordering oligos from commercial firms clearly saves time compared to synthesizing them in one's own lab; thus, screening by oligo suppliers may be the next best intervention point for preventing potential incidents of bioterrorism using synthesized DNA.

Description of options

Commercial DNA synthesis firms have no interest in supplying potentially harmful pieces of DNA to users who are not using them for legitimate research purposes or who may be unaware of danger to themselves or others.

Although it is certainly possible to synthesize a gene- or genome-length piece of DNA using a DNA synthesizer in one's own laboratory, the work can be accomplished more efficiently and accurately by firms that specialize in this service.

Below we present options to: 1) detect and thus prevent shipment of harmful genes or genomes, 2) detect people who place orders but have no legitimate need for such sequences, and 3) record these shipments for surveillance or forensic purposes.

Two general approaches are possible for screening DNA orders *prior* to synthesis. First, one can use computer software to compare the submitted DNA sequence to that of known pathogens. First-generation software for this purpose is available and already in use at several gene- and genome synthesis companies.[68] However, software improvements and a more refined list of potentially harmful genes and genomes would greatly enhance the effectiveness of computer-based screening. These research needs are discussed later in this section.

The entire responsibility and burden for screening does not have to fall on the commercial firms that synthesize DNA. The vast majority of their customers are employed by universities, research institutes, or private firms such as pharmaceutical companies. Most such institutions employ a trained biosafety professional. By requiring that biosafety professionals be part of the ordering process, one can ensure that all orders are from legitimate researchers working at known institutions and not from rogue individuals.

Finally, there is merit to storing information about previously placed orders for forensic purposes in the event of a bioterrorist attack. The sequence of the pathogen can be compared to past synthesis orders to identify potential matches.

In the following section, we first describe each of these options and then compare the advantages and disadvantages of each.

I-1. *Require commercial firms to use approved software for screening orders*

As mentioned above, commercial firms can use computer software to compare the DNA sequence submitted by their customers to the sequences of known pathogens. Several groups and individuals have proposed this option: first, George Church in a white paper;[69] and later the Synthetic Genomics Working Group of the National Science Advisory Board for Biosecurity;[70] members of the International Consortium for Polynucleotide Synthesis, an industry group of commercial DNA firms;[71] and many researchers in a Declaration of the Second Meeting on Synthetic Biology.[72]

First-generation screening software currently exists[73] and is being used by several firms today.[x] Firms that supply synthesized DNA could be required to use "certified" software that compares the sequence of submitted DNA orders to those of known pathogens.

As mentioned previously, commercial DNA synthesis falls into two rather distinct products: 1) synthesis of short oligonucleotides, typically up to about 100 bases long and 2) gene-length synthesis, producing pieces of DNA hundreds to thousands of base pairs long. Designing a screening system that is effective—both technically and administratively—for screening shorter, oligo-length pieces will be more of a challenge than designing one for gene-length pieces of DNA. Many short stretches of DNA from common genes look virtually the same in benign organisms and pathogens. Moreover, since oligos are used in a wide variety of different applications, the sheer volume of production of oligos far exceeds that for synthesis of genes and genomes. In addition, the turnaround times with which oligos are typically delivered is much shorter, making it more difficult to incorporate anything other than completely automated screening into the production process.

[x] Discussions about this and related approaches at Workshop 1 of this project based on commissioned paper from R. Jones.

Fortunately (at least with respect to bioterrorism), synthesizing a pathogen is more difficult and more time-consuming when starting with oligos than with gene-length pieces of DNA. Thus, screening could be required only for gene synthesis companies that supply longer sequences (for example, greater than 500 base pairs), or for all commercially synthesized DNA, regardless of length, including those from oligo suppliers. The strengths and weaknesses of this and other options are discussed separately for gene synthesis companies and for oligo suppliers in a later section.

For sequence screening to be effective, the FBI or similar agency must establish a procedure for commercial firms to follow in the event that a suspicious sequence is detected. Clearly, if the order is from a bioterrorist attempting to synthesize a pathogen, the FBI should be notified. However, the alarm might go off for two other reasons.

First, the specified DNA sequence might be very similar to one found in a benign organism as well. (Many genes, such as those that take care of basic metabolic functions, have close relatives in many organisms.) To avoid this situation, the screening software must be combined with a carefully constructed list of sequences that can detect pathogens of concern while avoiding false alarms.

The second type of false alarm is of a different nature. The DNA order might have been placed by a legitimate researcher from academia or a pharmaceutical company working with a dangerous pathogen to better understand the nature of the disease or its cure. If the software is working as designed, this type of alarm should far outnumber any other.

Thus, some method must be used to determine whether the order is from a legitimate researcher or not. Currently, firms that use screening software assume the responsibility of determining whether the order is being placed from a legitimate researcher. A type of identity check will add costs and administrative burdens the first time a researcher places an order with a firm, repeat orders from previously verified individuals would be processed more rapidly.

Note that for some DNA sequences, firms are *already* required to limit shipments to those researchers authorized to receive them. The Select Agent regulations cover transfers of synthetic DNA or RNA within the United States if the genetic material can be expressed as a select virus or toxin.[74] (This is, however, only a small portion of the total genetic sequence of all pathogens on the Select Agent list.)

Facilities sending and receiving Select Agent materials must be registered with either the Centers for Disease Control and Prevention (CDC) (for human pathogens) or the Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (for animal and plant pathogens), and each transaction must be reported. The NSABB has pointed out that even for this small subset of the Select Agent list, reporting requirements are not well understood by either commercial firms or the researchers themselves.

Finally, to ensure that legitimate laboratory workers fully understand the nature of the DNA that they have ordered, the results of screening should be sent to the researchers along with the synthesized DNA. While it is unlikely that potentially harmful sequence would be ordered and thus used inadvertently, it is certainly a possibility worth avoiding.

Firms that supply synthesized DNA could be required to use "certified" software that compares the sequence of submitted DNA orders to those of known pathogens.

I-2. ***People who order synthetic DNA from commercial firms must be verified as legitimate users by an Institutional Biosafety Officer or similar "Responsible Official"***

Rather than making the DNA synthesis firms responsible for verifying the identity of a researcher who places an order, this responsibility could be shifted to the research institutions where the scientists work. In particular, under this option, staff members that place orders

for synthetic DNA would have to be verified as legitimate users by the institution's biosafety officer. In order to accept an order, commercial firms would need to see that a registered institutional biosafety officer or otherwise-authorized institutional official had approved the individual researcher to place such orders.

The institutional biosafety officer would not have to screen each shipment for hazard. Rather, the biosafety officer would merely verify that the person ordering the DNA was a legitimate user of synthetic DNA. Such approval might need to be reviewed once per year and might be linked to biosafety certification or training requirements. A list of verified researchers could be maintained and updated electronically so that individual orders could be approved with minimal time delay.

This approach is somewhat similar to that used by the American Type Culture Collection (ATCC), a nonprofit organization that stores and distributes biological materials such as cell lines, bacteria, animal and plant viruses, and antisera. ATCC will only ship potentially hazardous material with the approval of a registered biosafety professional. Likewise, shipments of radioactive materials can only be received by those who are licensed by the Nuclear Regulatory Commission (or equivalent state regulatory body) to receive them.

Rather than making the DNA synthesis firms responsible for verifying the identity of a researcher who places and order, this responsibility could be shifted to the research institutions where scientists work.

Lists of verified users could be maintained either by each institution or by a centralized third party. Under the latter approach, institutional officers would submit lists of legitimate users to an Internet-based verification company such as VeriSign, which would issue "electronic certificates" to those users. This would minimize the administrative burdens to both the institutions and synthesis firms, and because the verification would occur electronically, allow virtually instantaneous approval.

A biosafety officer, at his or her discretion, might choose to screen individual orders as well, examining the research from the perspective of laboratory safety, potential harm to the environment, or consistency with a researcher's lines of experimental inquiry. Clearly, however, examining each order individually would add to his or her workload and might slow down the approval process considerably.

I-3. ***Commercial firms must use approved software for screening orders; people who place orders must be verified by a registered Institutional Biosafety Officer***

Yet another option is to combine options I-1 and I-2. Under this hybrid approach, to place an order for synthesized DNA, a researcher would have to be verified as a legitimate user by a biosafety official, and commercial DNA suppliers would also be required to screen the orders for hazardous sequences.

The biosafety official would be asked to create two lists of researchers: 1) legitimate users of synthetic DNA, and 2) the subset of those researchers who are conducting experiments with pathogens or with DNA derived from a pathogen. In the event that an order submitted by a legitimate user of synthetic DNA was identified by software screening as potentially hazardous, but that researcher had not been approved by the biosafety official to use potentially hazardous DNA, the biosafety official would have to be consulted before the DNA order could be filled.

The biosafety official preparing these lists might be either the institutional biosafety officer or the chair of the Institutional Biosafety Committee (IBC). IBCs were created under the National Institutes of Health (NIH) Guidelines for Recombinant DNA Research to assess the biosafety and environmental risks of proposed recombinant DNA experiments conducted in academic and commercial settings, and to decide on the appropriate level of biocontainment.

In addition, shipments of certain types of hazardous genes or portions thereof, instead of being shipped directly to the individual researcher, might be sent to the institutional

biosafety officer or to the chair of the IBC. For example, commercial firms could be required to send synthesized DNA longer than 500 base pairs whose sequence matches that of a gene on the hazardous list only to approved institutional biosafety officials, rather than directly to the researcher who placed the order.

I-4. ***Require commercial firms to store information about customers and their orders***

A far more minimalist approach would be simply to require commercial firms to store information about customers and their orders. The Toxic Substances Control Act (TSCA) already requires firms to retain records, including the identity of the customer, for many types of chemicals and other substances (including, in some cases, DNA sequences) for at least 5 years, but it does not appear that this requirement has been applied to firms making synthetic DNA.

Commercial DNA suppliers would be required to register with a designated agency such as the FBI. Information about each order would be stored at the firm for a specified period of time and would be made available to the FBI under certain specified conditions, such as the aftermath of a biological attack. In that event, once the pathogen used in the attack had been isolated and sequenced, its sequence could be compared to orders for synthesized DNA to try to find a match.

To ensure that orders could be associated with individuals, firms might not be allowed to deliver synthesized DNA to anonymous Post Office boxes. (FedEx has a similar requirement.) Although the association between the shipping address of an order and a bioterrorist attack to which that order may have contributed does not necessarily mean that the individuals responsible for the order had anything to do with an attack, such an association could nevertheless provide a powerful investigative tool.

Comparing the Options

Options for Gene Synthesis Companies

The primary purpose for implementing any of the first three options above is to prevent a potential bioterrorist from obtaining DNA from a commercial firm. The fourth option, rather than focusing on prevention, might help law enforcement officials respond to an incident, should it occur.

Options Table IA below summarizes our judgments about how well each of the options would enhance biosecurity if implemented at gene synthesis companies; that is, firms that produce gene- and genome-length stretches of DNA. The Table also includes our evaluation of each option's effectiveness for meeting two other important goals: improving laboratory safety and protecting the environment. Finally, the Table compares the options according to a series of other important considerations, such as the costs and difficulties of implementation. In a later section, we discuss the effectiveness of these options when implemented by firms that produce shorter oligonucleotides.

Relative effectiveness for achieving goals

For preventing bioterrorists from obtaining long stretches of a potentially pathogenic genome, we judge Option I-3, the hybrid approach, to be the most effective; followed by Option I-1, screening by approved software; and finally Option I-2, requiring that customers be verified as legitimate users of synthetic DNA by their institution's biosafety officer. Option I-3 melds the strengths of the other two options. Screening software will identify potentially harmful pieces of DNA, regardless of whether the intended use is nefarious or legitimate. Verification from an institutional biosafety officer is a simple way of determining whether the customer appears to be a legitimate user of that potentially harmful piece of DNA.

A far more minimalist approach would be simply to require commercial firms to store information about customers and their orders.

Option I-3 is likely to be the most effective option for avoiding harmful laboratory accidents and releases to the environment. Under this option, a biosafety officer would be notified if a user who has not been verified to use pathogenic sequences in his or her research ordered one or more such sequences, either inadvertently or deliberately. Option I-1 (screening alone) might avoid some accidental orders of harmful sequences, but it would likely be less effective.

By requiring firms to store information about orders for several years and to supply that information to the FBI in the event of a bioterrorist attack (Option 4), it might be possible to identify the individual or group responsible for an attack with a synthetic organism. This option might also be used in the event of an accidental release of a synthetic organism into the environment. Such records would provide one of very few possible leads for identifying the perpetrating individuals or groups "after the fact." Moreover, the knowledge that such orders would be revealed after an attack could deter any would-be terrorist from placing such orders for hazardous DNA with commercial firms, forcing him or her to utilize more difficult means for obtaining the pathogen.

Relative effectiveness on other criteria

While effectiveness in achieving goals is extremely important, policy choices must be made with other criteria in mind. An option whose costs exceed its benefits, or that hampers legitimate researchers more than bioterrorists, is not likely to be chosen.

The bottom half of Table IA displays our judgments of the effectiveness of each of the four options in meeting a series of other important criteria. For example, the first row examines the ***costs and burdens of each option to government and to DNA synthesis firms***. Note that the costs and burdens of the first three options are inversely proportional to their effectiveness for preventing a bioterrorist attack. We judge Options I-2 and I-3 to be somewhat burdensome, and while we believe that Option I-3 would be the most effective for preventing a potential attack, it is likely to be the most costly and burdensome to implement.

Options I-1 and I-3, both of which rely on computerized screening of orders, will require several additional components to work effectively. First, a list of dangerous pathogens (e.g., Select Agents) and potentially harmful genes (e.g., for antibiotic resistance) must be prepared. Such lists might be compiled by a U.S. government agency such as CDC, which administers current regulatory controls on dangerous human pathogens; the Department of Homeland Security; or perhaps by an advisory body that is sanctioned by either of those agencies.

Second, the same agency would also be responsible for testing and certifying the screening software, although this task might also be delegated to an advisory group.

Third, commercial gene synthesis companies would be required to register with the implementing agency and certify that approved software is being used. That agency might also perform periodic random tests to determine whether the software was, in fact, in use.

Finally, the FBI or a similar agency must establish a "hotline" for commercial DNA synthesis firms to call when they detect a suspicious sequence. That agency would need to establish thresholds of concern to determine when firms should call the hotline and reject a suspicious order.

The ***need for additional research*** is a second important consideration listed in Options Table IA. For Options I-1 and I-3 to be effective, two technical improvements are crucial: better screening software and a tailored list of risky sequences against which orders will be screened.

The software itself must be improved to identify risky orders more effectively and ef-

ficiently. Both the error rate and the amount of additional human screening required must be reduced.

Improvement is also needed in the list of harmful genes and genomes to which the submitted sequence is compared. The current software relies on the Select Agent list, which was designed for an entirely different purpose: to restrict *physical* access to a list of pathogens that could be used as bioweapons.

The combined DNA sequence of all pathogens on the Select Agent list may not provide the most effective basis for screening software. For that purpose, additional pathogens might be included. The DNA sequence of individual genes of concern could also be added, such as virulence genes or genes that confer certain types of antibiotic resistance (perhaps limited, for example, to third-line or other critical antibiotics).

Moreover, some DNA sequences found in select agents are not very useful for screening. The sequences of some metabolic genes are largely conserved throughout a wide variety of organisms, making them poor candidates for distinguishing pathogens from benign organisms. To help avoid false alarms, the screening list may have to be divided into two sublists: DNA sequences that are found only in pathogens, and DNA sequences that are found both in pathogens and in benign organisms. Regulatory sublists may also be required. As mentioned above, some pieces of DNA are already subject to the requirements of the Select Agent regulations. Commercial firms need to know those sequences for which additional regulations apply.

Yet another important consideration is the extent to which each option ***impedes or burdens legitimate research*** while seeking to prevent illegitimate uses or accidents. All of the options fare reasonably well on this criterion. Software screening will increase the cost of gene synthesis somewhat, but not by very much. Several firms already screen today for select agents and remain competitive.

Verification of legitimate users by an institutional biosafety officer would add a new approval step. Each order would not have to be verified; instead, individual researchers would be verified as legitimate users perhaps once a year, or until the relevant biosafety officer indicated that certain users should no longer be authorized to order synthetic DNA (perhaps because they had left the institution). Within universities or other large research institutions with biosafety officers, this extra step would add to the administrative burden but should be readily accommodated.

The greatest impact would be felt by researchers working for small start-up firms that do not have a biosafety officer. In such cases a mechanism would have to be established to allow such scientists to be verified by independent consultants. (Independent consultants are already being used by smaller institutions to help accomplish NIH-required and other reviews of human subjects research and research with animals.) Nevertheless, if such a review mechanism were too burdensome, small start-up firms might shift to in-house DNA synthesis instead.

None of the options are effective for ***promoting constructive applications***, though there might be some modest benefit to the added interaction between researchers and biosafety officers.

The current screening software relies on the Select Agent list, which was designed for an entirely different purpose: to restrict physical access to a list of pathogens that could be used as bioweapons.

Options for Firms that Synthesize Oligonucleotides

Options Table IB displays our judgments about the effectiveness of requiring firms that synthesize oligonucleotides to adopt one or more of these options. Again, oligonucleotide suppliers synthesize and sell pieces of DNA typically shorter than 100 bases long. In general, while implementing these options at oligo supply firms will certainly add another layer of protection, the risk reduction per unit of effort would be lower for these firms than for suppliers of longer gene and genome stretches of DNA.

Options Table IA: Summary of Options for Gene Synthesis Firms

Does the Option:	IA-1. Gene firms must screen orders	IA-2. Biosafety officer must verify people who place orders	IA-3. Hybrid: Firms must screen and biosafety officer must verify people	IA-4. Firms must store information about orders
Enhance Biosecurity				
by preventing incidents?	◉	○	●	○
by helping to respond?	—	—	—	○
Foster Laboratory Safety				
by preventing incidents?	○	—	○	—
by helping to respond?	—	—	—	—
Protect the Environment				
by preventing incidents?	○	—	○	—
by helping to respond?	—	—	—	○
Other Considerations:				
Minimize costs and burdens to government and industry?	○	○	○	●
Perform to potential without additional research?	○	●	◉	○
Not impede research?	◉	◉	○	●
Promote constructive applications?	—	—	—	—

Key to Scoring:

- ● Most effective for this goal. Most effective performance on this consideration.
- ◉ Relatively effective.
- ○ Moderately effective.
- ○ Somewhat effective.
- ○ Minimally effective.
- — Not relevant.

Relative Effectiveness for Achieving Goals

As can be seen by comparing Options Tables IA and IB, implementing Options 1 and 3 at oligo supply firms would be significantly less effective for preventing incidents of bioterrorism than the same option implemented at gene synthesis companies. This conclusion is based on two factors. First, the shorter the piece of desired DNA, the lower the confidence that the particular sequence is found exclusively in a pathogenic organism and is not present in a benign organism as well. Options 1 and 3 rely on computer software to distinguish potentially harmful from benign pieces of DNA. When the results are ambiguous, the only solution is to request a review of the data by a knowledgeable staff member. Next-generation software might be able to clarify these cases to some extent, but a degree of ambiguity is inevitable for very short pieces of DNA.

Moreover, because oligo-length stretches of DNA have many applications other than synthetic genomics, the amount of risk reduction per unit of screening effort will be low. For oligo synthesis, not only is the needle in the haystack that one is searching for shorter, but the haystack is larger as well.

Thus, for preventing potential bioterrorists from synthesizing a harmful organism from commercial oligos, we are hard-pressed to determine whether software-based screening (Option I-1) is superior to having biosafety officers verify legitimate users (Option 2). Option I-3, combining the strengths of both Options I-1 and I-2, is again clearly the most effective approach. Option I-1 and Option I-3 —those that rely on screening—are the most effective for fostering laboratory safety and protecting the environment.

Relative Effectiveness on Other Criteria

The pattern of relative effectiveness of these options in meeting the other important criteria listed in Options Table IB generally follows that described above for the options implemented at gene synthesis companies. In many cases, however, implementing these options at oligo houses would be less effective or desirable.

The costs and burdens of screening for industry will be higher at oligo supply firms than at gene synthesis companies on a per-unit or per-dollar of business basis because the "false positives" that must be resolved will be more frequent with shorter sequences. Similarly, software-based screening options require more research and development to be effective for screening shorter-length oligos. The far wider variety of uses for oligos than for genes and genomes means that many more scientists will be inconvenienced by regulations applied to oligo supply houses. Finally, none of these options is effective at promoting constructive applications by researchers.

The costs and burdens of screening for industry will be higher at oligonucleotide supply firms than at gene synthesis companies because the "false positives" that must be resolved will be more frequent with shorter sequences.

Additional Concerns

Two additional considerations merit discussion, although they are difficult to rate qualitatively as we do in the sections above. These issues are the ability of each of the options to function successfully in an international context and their ability to keep pace with rapidly changing science and technology. The comments below apply to options for both gene synthesis companies and oligonucleotide suppliers.

Thinking past the U.S. border

All of the options will lose effectiveness if implemented in the United States alone; hence, international harmonization would be desirable. Today, the majority of gene synthesis firms are located within the United States and Europe. Customers can be located anywhere in the world. Import rules might be able to limit the amount of DNA synthesized in other countries that is shipped to the United States. But none of the options could address the potential problem of a synthesized pathogen that is smuggled across a U.S. border.

Options Table IB: Summary of Options for Oligonucleotide Synthesis Firms

Does the Option:	IB-1. Oligonucleotide manufacturers must screen orders	IB-2. Biosafety Officer must verify people who place orders	IB-3. Hybrid: Firms must screen and Biosafety Officer must verify people	IB-4. Firms must store information about orders
Enhance Biosecurity				
by preventing incidents?	○	○	◉	○
by helping to respond?	—	—	—	○
Foster Laboratory Safety				
by preventing incidents?	◯	—	◯	—
by helping to respond?	—	—	—	—
Protect the Environment				
by preventing incidents?	—	—	—	—
by helping to respond?	—	—	—	○
Other Considerations:				
Minimize costs and burdens to government and industry?	○	○	○	●
Perform to potential without additional research?	○	●	○	○
Not impede research?	○	○	○	●
Promote constructive applications?	—	—	—	—

Key to Scoring:

- ● Most effective for this goal. Most effective performance on this consideration.
- ◉ Relatively effective.
- ○ Moderately effective.
- ◯ Somewhat effective.
- ◯ Minimally effective.
- — Not relevant.

Option I-1, computer screening of orders, is among the easiest of these options to harmonize internationally. Lists of pathogens of concern vary somewhat by country as do reporting rules and requirements, but the software modifications to handle such differences would be modest. Option I-4 would also be quite straightforward to implement internationally if archived sequence information were shared not only with national law enforcement agencies under some specified set of conditions, but also with international partners. Such sharing might well be possible, given the already considerable amount of information sharing that occurs among intelligence agencies around the world. However, the intensely proprietary nature of some gene orders, together with concerns about linkages between foreign intelligence agencies and their countries' firms, might make such international information sharing among countries politically unacceptable.

International harmonization under Option I-2 would rely on the framework of biosafety rules in place in each of many different countries. Though it would not be impossible to identify and certify responsible officials at research institutions around the world, the differences among national biosafety frameworks would make harmonization a challenge. Option I-3, a combination of Options I-1 and I-2, would thus be as difficult to harmonize internationally as Option I-2 alone.

Keeping pace with evolving science and technology

Options I-1 and I-3, which rely on software screening, will have the greatest difficulty keeping pace with rapidly changing science and technology. Today, synthesizing a small viral genome as it exists in nature is still a challenge, so that screening tools can focus on known DNA sequences. In the not-too-distant future, however, scientists may be able to modify pathogens so that they are not as easily detected. Software screening tools will then have to recognize the genetic mechanisms behind virulence, rather than simply matching DNA sequences.

Perhaps an even greater challenge will occur if laboratory benchtop synthesizers improve in ease of use and quality of product to the point where they are as simple to use as ordering from a commercial firm. The next section discusses options that apply to laboratory DNA synthesizers.

II. Policies for monitoring or controlling equipment and reagents

Description of this intervention point

If a bioterrorist could not simply mail order the desired genes or oligonucleotides to construct a pathogen, the next approach he or she might try would be to construct the genome from scratch. This would involve producing oligos using a DNA synthesizer, followed by assembly of the oligos into the genome of interest. At a minimum, the synthesis step would require the acquisition of an oligonucleotide synthesizer (purchased or built) and a relatively small set of chemicals.

In attempting to monitor or control the equipment or materials needed to synthesize DNA, the most readily accessible intervention point would be at the level of the DNA synthesizer itself. (See Figure 1, Panel B for a photograph of a laboratory benchtop synthesizer.) DNA synthesizers produce short segments of DNA with specified sequences of the four DNA bases (A, T, G, and C). The device automates the series of chemical reactions needed to add a specific base to an existing strand of DNA, repeating the process as many times as necessary with the appropriate reagents until the desired base sequence is complete.

DNA synthesizers range in size from that of a microwave oven to that of a refrigerator, cost anywhere from a few thousand dollars or even less (used) to over a hundred thousand dollars (high-end, new), and can typically produce tens to hundreds of different DNA sequences at a time. At least 15 firms in the United States and at least an additional seven worldwide sell new or refurbished DNA synthesizers. Tens of thousands of these machines have been manufactured, and they are available not only from scientific supply vendors but also used on the aftermarket, including on the auction site eBay.

Similar to ordering short pieces of DNA from a commercial supplier, short oligonucleotides must be "cleaned up" and assembled in the proper order to form gene- or genome-length strands of double-stranded DNA.

Description of Options

Methods to monitor or control DNA synthesizers include ***registration*** (a requirement to notify the government when selling, buying, or otherwise possessing a DNA synthesizer) and ***licensing*** (government permission is needed before a DNA synthesizer can be acquired or retained). Registration or licensing of a synthesizer could also be made a requirement for procuring ***specialized raw materials*** (especially the phosphoramidite precursors) necessary for synthesis, ***key spare parts*** of synthesizers (such as the capillary tube assembly), and ***service contracts for synthesizers***, which would make it more difficult to operate synthesizers that were not incorporated into this regime.

Forcing individuals with illicit intent to obtain DNA synthesizers surreptitiously, or to build their own synthesizers would complicate their planning, opening up additional possibilities for detection.

Any of these options would assign to each synthesizer an official owner of record who would have responsibility for that machine. This list of owners of record would identify to the government the people or institutions authorized to synthesize DNA. Discovery of a synthesizer that had not been registered or licensed would constitute ***prima facie*** grounds for suspicion.

These options would enhance security by impeding illegitimate activity and by helping to expose it. Forcing individuals with illicit intent to obtain DNA synthesizers surreptitiously, to lie to governmental authorities, or to build their own synthesizers would complicate their planning, open up additional possibilities for detection, and provide unambiguous grounds for prosecution if they are caught. Use of an ostensibly legitimate synthesizer for illegitimate purposes might be detected or deterred more easily if all synthesizers were declared and accountable to specific owners of record. However, registration or licensing of synthesizers would also impose some costs and regulatory burdens for legitimate users and for government.

In effect, these measures would serve as what the arms-control community calls a "confidence-building measure"—a measure that is meant to give an indication of good intent but that cannot provide reliable proof of compliance. One major difference between legitimate and illegitimate users of biology and biotechnology is that legitimate users should be willing to reveal their activities, within limits, whereas illegitimate users would seek to conceal theirs.

II-1. *Registration of DNA synthesizers*

Newly manufactured or imported synthesizers would be given unique identifiers, and manufacturers, importers, and distributors would collect and report to the government information about the purchasers of these machines. Criteria would also have to be developed to specify how and when custom-built synthesizers would have to be registered.

If such a regime were implemented comprehensively, it would have to include all existing DNA synthesizers and not just newly purchased ones. On the other hand, the regime might be designed to capture only new and presumably more capable synthesizers, leaving the older machines unregulated. Such a system would be easier to administer, albeit

less complete. In either case, there would need to be provisions for formally decommissioning machines as they were retired, and for re-registering them when they were sold or transferred. Failure to register might incur administrative or even criminal penalties, without the need to prove illegitimate intent. Registrations could, but need not, be made a matter of public record. Providing public access to registration information would increase the transparency of DNA synthesis activities and give private citizens and interest groups some ability to monitor them. This ability to monitor would be particularly attractive to outsiders who are interested in what firms and research institutions are doing with DNA synthesizers, and who may suspect that these institutions would prefer to keep their activities out of public view. By the same token, such monitoring may not be welcomed by the firms and research institutions conducting DNA synthesis, who may not consider their use of such devices to constitute a waiver of the right to protect proprietary information.

II-2. *Licensing of DNA synthesizer owners*

In the case of licensing, the procedures would be similar to those for registration, with the additional element that the government could specify the criteria required of registrants and could deny licenses to applicants who did not meet the criteria. Such a system would be similar in concept, if not detail, to the current system under which individuals must be granted permission by the U.S. government to have access to select agents.

Note that a regime that did not "grandfather" all existing DNA synthesizers raises the possibility that an individual or institution could be denied a license for equipment that it already possessed, making its continued possession illegal and forcing its divestiture.

II-3. *Licensing of synthesizer owners, plus license required to procure reagents or services*

Any controls on DNA synthesizers would be strengthened by additional controls that would prevent those with unregistered or unlicensed machines from being able to procure key reagents, such as the phosphoramidites that DNA synthesizers convert into oligonucleotides. However, such controls would be complicated by the fact that although DNA synthesis is absolutely dependent on phosphoramidites, synthesis forms a negligible share of the market for them. Pharmaceutical companies use these materials to produce drugs such as AZT (a treatment for HIV infection) in amounts that are orders of magnitude greater than those required for gene synthesis. On a yearly basis, individual laboratories or gene synthesis firms might consume grams or a few kilograms of phosphoramidites respectively whereas pharmaceutical manufacturers use thousands of kilograms of phosphoramidites per year.[75] For a material control system on these materials to be consistent, these vastly larger customers would have to be brought into the regime and required to register before getting permission to purchase phosphoramidites, and penalties would have to be applied to those who re-transferred the controlled commodities to unregistered users. However, it would be extremely difficult to enforce such a regime with a precision needed to detect the diversion of the grams of material involved in DNA synthesis out of the many thousands of kilograms of material consumed for pharmaceutical purposes.

It would be easier to implement a system in which unregistered or unlicensed synthesizers would be ineligible to be serviced, although it would similarly be difficult to ensure that all individuals or firms capable of servicing synthesizers would comply with such a requirement.

Comparing the Options

Relative effectiveness for achieving goals

The options discussed above are intended only to ***enhance biosecurity***. However, the security benefits would be modest because no such regime could have high confidence in preventing illegitimate synthesis. Options Table II below summarizes the potential contributions of the various options to enhancing biosecurity.

Option II-1, registration, and Option II-2, licensing of equipment, are only minimally to somewhat effective for enhancing biosecurity. Synthesizers are relatively small and, at present, easy to acquire and hide. It would be very difficult to ensure that all existing synthesizers were identified and brought into a registration/licensing regime. Likewise, it would not be physically difficult to possess, maintain, and operate an unregistered machine unless airtight controls could be placed on the necessary raw materials (Option II-3).

A more serious security liability than unregistered synthesizers, however, is the possibility that registered synthesizers could be used for illicit purposes.

It is worth noting that synthesizers can be built from scratch, although with significant reductions in throughput and efficiency compared with a purchased product.[76] There are few externally observable indicators (other than supply of reagents) that would denote the existence or operation of an unregistered synthesizer. Therefore, Option II-3, requiring that materials or maintenance be provided only for synthesizers that are licensed would increase still further the difficulty of operating unregistered machines.

A more serious security liability than unregistered synthesizers, however, is the possibility that registered synthesizers could be used for illicit purposes, either by the registrants themselves (i.e., an apparently legitimate firm set up as a cover for illicit activity) or by individuals who have access to legitimately registered machines (e.g., employees of a firm or students at a university). It would be difficult for an owner of record or any governmental authority to monitor the usage of registered DNA synthesizers closely enough to detect such illegitimate activity as it was taking place. Moreover, any attempt to do so would likely mitigate much of the motivation for preferring in-house synthesis over contracting out for gene synthesis in the first place (i.e., ease of use, rapid turnaround time, and absolute confidentiality).

Option II-1, a registration requirement, might succeed in deterring synthesis by individuals or organizations so intent on maintaining secrecy that they would not be willing to register for use with their real names. (Obviously, the identities of registrants or licensees would have to be validated to prevent them from using false names.) Option II-2, licensing, would potentially have greater biosecurity value than registration in that it would not only ban synthesis by unlicensed users but would give the government the authority to limit who can be licensed. This ability could be important if the government had intelligence identifying individuals who sought to abuse DNA synthesis. As with the Select Agent Rule, it would be possible to subject all individuals seeking routine access to a DNA synthesizer to a security vetting procedure, such as fingerprinting and checks against criminal and terrorist databases.

It is difficult to say how effective the existing Select Agent restrictions have been at impeding anyone from obtaining pathogens for illicit purposes. Of 14,724 individuals for whom the CDC was asked to grant access to Select Agents, 107 were identified as "restricted persons" and denied approval. Of those 107, one was denied on the basis of being "reasonably suspected by any Federal law enforcement or intelligence agency of having knowing involvement with an organization that engages in domestic or international terrorism."[77] There is no way of knowing whether anyone has been deterred from seeking access to select agents for fear of being turned down. Nevertheless, there would be little reason to prefer licenses to registration unless the authorities had the

Options Table II: Summary of Options for Monitoring or Controlling Equipment or Reagents

Does the Option:	II-1. Owners of DNA synthesizers must register their machines	II-2. Owners of DNA synthesizers must be licensed	II-3. Licensing of equipment, plus license required to buy reagents and services
Enhance Biosecurity			
by preventing incidents?	○	○	◎
by helping to respond?	○	○	○
Foster Laboratory Safety			
by preventing incidents?	—	—	—
by helping to respond?	—	—	—
Protect the Environment			
by preventing incidents?	—	—	—
by helping to respond?	—	—	—
Other Considerations:			
Minimize costs and burdens to government and industry?	●	◉	◎
Perform to potential without additional research?	●	●	◉
Not impede research?	◉	◎	○
Promote constructive applications?	—	—	—

Key to Scoring:

- ● Most effective for this goal. Most effective performance on this consideration.
- ◉ Relatively effective.
- ◎ Moderately effective.
- ○ Somewhat effective.
- ○ Minimally effective.
- — Not relevant.

legal authority to deny them on the basis of information suggesting that an applicant was seeking to use DNA synthesizers for illegitimate purposes.

By establishing an owner of record for each synthesizer, all three options would serve to make the operators of these machines more accountable for what is done with them. Therefore these policies may serve in part to promote responsible use of the machines, helping to foster a climate in which laboratories operate more safely and accidental releases are minimized. However, any such biosafety benefits would be quite indirect.

Registering or licensing synthesizers would be of very limited utility in responding to the accidental or deliberate release of an organism constructed with synthesized DNA. Unlike bullets, which can be associated uniquely with the gun that fired them, pieces of synthesized DNA cannot be attributed to a particular synthesizer. Authorities investigating the release of a biological agent possibly incorporating synthesized DNA might find a list of registered DNA synthesizers helpful in identifying the locations known to have the capability of synthesizing DNA. Nevertheless, such a list would be far less useful than the sequence-specific information available about commercially synthesized DNA under Option I-4.

Relative effectiveness on other criteria

The bottom half of Options Table II is our evaluation of the effectiveness of each option with respect to other considerations. The ***costs and burdens to government and industry*** would be minimal in a regime requiring only the registration of synthesizers; the same applies to licensing though somewhat less so. In both cases, however, the paperwork and tracking issues would be relatively straightforward compared to Option 3, requiring registration to purchase reagents. Because of the large volume of reagents used in DNA synthesis that are also consumed for other purposes (e.g., in pharmaceutical production), a registration requirement to purchase reagents would confer a significant burden to a larger number of users, as well as the agency tracking such registrations. To reduce this burden, however, it might be possible to issue waivers to pharmaceutical companies that use phosphoramidites exclusively for applications unrelated to DNA synthesis.

Other aspects of implementing these options may also impose minor burdens, but would require no ***additional research***. Neither the registration nor the licensing of synthesizers would require research per se; the identities of companies that manufacture and supply synthesizers are known. Although it might be helpful to have a list of the serial numbers of every synthesizer ever made commercially, at least initially such information would not be required. With respect to requiring registration for the purchase of reagents, additional information might be required. For example, it would be useful to pinpoint the sources of phosphoramidites and other reagents used in DNA synthesis. Because many of these raw materials are manufactured outside the United States, it might be difficult to compile a complete list of suppliers.

Modest paperwork and record-keeping would be involved in transferring registration during the purchase, sale, or resale of synthesizers, and in verifying that purchasers of materials or services were legitimate users. Licensing could be considerably more complicated, depending on the information and processing time required by licensing authorities and the likelihood of misleading data (such as a false entry on a terrorism watch list) that incorrectly indicated an increased risk of illegitimate use. In either case, a registration or licensing requirement could ***impede research*** to some degree as these paperwork issues were dealt with.

Additional concerns

Thinking past the US border

A registration or licensing scheme could be implemented solely with respect to synthesizers produced within or imported into the United

States. Because the markets for synthesizers and reagents are inherently international, however, such a regulatory regime would become more useful (in terms of capturing synthesizer capability) the more widely it was deployed around the world, which would require that other countries enact equivalent policies. In that case, harmonized requirements among different national systems would be desirable, both in terms of imposing equivalent burdens on researchers and manufacturers worldwide and in minimizing the burden that vendors and distributors face in tailoring export policies to specific destinations. It is not likely that the cost or burden of implementing a registration regime would be severe enough to drive research out of a country that imposed such a regime. Still, it is conceivable that an onerous and inappropriate licensing process—particularly one that excluded significant numbers of applicants—could induce researchers to seek work in countries that do not impose such regulations.

A licensing regime may be more difficult to harmonize internationally than a registration regime, since different countries may adopt different criteria for who should or should not be licensed. For example, the United States bans access to select agents, without exception, to nationals of countries on the State Department's list of "state sponsors of terrorism." This particular list is unlikely to be adopted even by other nations that agree to impose nationality tests for access to synthesizers, since countries will find it very hard to agree on whose nationals pose unacceptable risks. Also still to be determined is how internationally harmonized security standards for granting access to DNA synthesizers would be negotiated.

International harmonization would be more important to a regime that regulated access to key reagents than it would be to a regime that regulated only the synthesizers themselves. Given that the producers of the key reagents used in DNA synthesis are located for the most part outside the United States, there would be little hope of effectively controlling access to these materials without the cooperation of the countries in which the suppliers are located. Of course, controls on reagents could be imposed on a strictly domestic basis in the United States for the purpose of providing an incentive to register U.S.-based synthesizers. If imposed unilaterally, however, such controls would not be effective in impeding those with unregistered synthesizers from acquiring the necessary reagents directly from foreign sources unless effective import controls on those reagents were also imposed.

Keeping pace with evolving science and technology

One area in which policies governing synthesizers could evolve in the future would be to implement a requirement for DNA synthesizers to keep tamper-proof archives of every sequence that had been synthesized for possible access by government investigators after a bioterrorism incident. Such an option would be analogous to option I-4, proposed above, that would require commercial synthesis firms to archive the DNA sequences of all their shipments. However, the utility of such a scheme and the difficulty of implementation differ in these two cases. A DNA synthesis firm would have no incentive to frustrate or evade an archiving requirement, whereas a terrorist operating a DNA synthesizer would have every reason to do so, and (since the machine would be in his or her possession) the means to try. As a result, it would be much more technically challenging and disruptive to the industry to build a reliable, tamper-proof archival capability into all DNA synthesizers than it would be for commercial firms to keep track of their orders.

Moreover, in the near-term, we do not believe that the use of DNA synthesis is as attractive to would-be bioterrorists as other means of acquiring or developing potential bioterrorist agents. Therefore, we judge that for the next few years, the security benefit of requiring synthesizers to securely archive their sequences would be too low, compared to the difficulty and disruption that such a requirement would impose.

Because the markets for synthesizers and reagents are inherently international, a regulatory regime would become more useful the more widely it was deployed around the world.

However, we also acknowledge that in the future, synthesis of many dangerous pathogens will become considerably easier than other means of acquiring such agents for malicious use, at which point the relative security value of implementing an archiving requirement for synthesizers may grow to the point that policymakers may wish to consider it.

III. Policies for the roles of users and organizations in promoting safety and security in the conduct of synthetic genomics protocols

Description of this intervention point

The focus of this intervention point is the user of DNA synthesis technology and the institutions, organizations, and extra-institutional communities that support and oversee such work. Unlike the options identified for other intervention points, these options apply only to legitimate users of DNA synthesis technology and do not, therefore, directly support biosecurity measures aimed at frustrating illegitimate use. Indirectly, these options may have positive implications for biosecurity. Collectively, the options address how users are trained, how the safety of their work is judged, and how standards of practice can be enforced either informally or formally.

Legitimate researchers carry out their work with the assumption that they are pursuing constructive lines of inquiry and that their research will seek to benefit society. In order to carry out their work, scientists and engineers (especially, although not exclusively, at universities) have at their disposal a number of support mechanisms that provide guidance or enforce rules. With appropriate training and practice, investigators know the resources available to them and the rules they need to follow. By encouraging and using the potentially close relationships between researchers and the bodies that guide them, it should be possible to develop safer laboratories and reduce the risk that synthetic pathogens are released accidentally. Further, prior review of experiments could help steer researchers away from lines of research that are potentially dangerous with respect to biosecurity. Although these options are proposed for synthetic genomics research, they include elements that could apply to all microbiology laboratories.

The current biosafety framework is in large part due to the foresight of the scientists who invented recombinant DNA- and related technologies thirty years ago. Any new framework for managing security risks arising from advances in DNA synthesis technologies must build on these existing practices, which have enabled the demonstrably safe development and application of recombinant DNA technology over the past three decades.

In considering how best to build on the existing biosafety regime, it is useful to recognize two characteristics of the communities that are using DNA synthesis technologies today. First, many of the individuals involved in developing and applying DNA synthesis technologies are not life scientists. Many come from various branches of engineering and some are from the physical sciences and the social sciences and humanities. Second, the conversations that led to development of today's biosafety framework took place a generation ago, and are largely unknown to many practitioners and almost all students in engineering and science. Taken together, these points indicate both the need and the opportunity for developing a constructive culture, in which developers, practitioners, and consumers of gene and genome synthesis technology work together to address the social issues associated with the technology itself.

Description of Options

We have identified six options to enhance the safety and security of legitimate uses of synthetic genomics. Some rely on self-governance from within the scientific community, for example, education of trainees by senior researchers. Others rely on outside involvement in governance. Some of the options include penalties for non-compliance, but many of them establish a norm that legitimate researchers would be expected to follow during their professional research activities and that, if violated, would identify the transgressor as irresponsible.

The first three options (education, a safety manual for synthetic biology, and a clearinghouse mechanism for best practices) involve institutions and/or individual experts outside the immediate community of synthetic biologists e.g., university administrators, CDC, and NIH. Another approach to implementing the first three options would be through a professional society. Although there are at least four professional societies for bioengineering or biomedical engineering in the United States alone, none of these societies has yet developed standards of practice for engineers whose work involves the intentional manipulation of genetic material. More than thirty years after Asilomar, there is no "American Society of Genetic Engineers" or similar body. Given the growing interest in developing biology as a technology, and the expanding capabilities for doing so, including synthetic genomics, this new research community might consider establishing a new organization that explicitly supports activities such as professional education or the licensing of practicing biological engineers.

III-1. *Education about risks and best practices as part of college and university curricula*

Education about the risks of synthetic genomics and training in laboratory best practices could be provided for undergraduates, graduate students, and even faculty who have been working in other fields and now wish to conduct research in synthetic genomics. Further training in research ethics, the societal implications of science, and related aspects of law would also be helpful. Although the precise mechanisms could vary, the general approach would be to educate students about biosafety and biosecurity issues at the same time that they are being introduced to experimental concepts in synthetic genomics.

The current biosafety framework is in large part due to the foresight of the scientists who invented recombinant DNA and related technologies thirty years ago.

Students must be made explicitly aware of the need for biosecurity measures such as the screening of DNA sequence orders or about what might constitute suspicious activities in the laboratory. Another issue that would have to be included in a synthetic genomics curriculum is that of "dual-use research of concern" discussed by both the Fink Committee and the National Science Advisory Board for Biosecurity.[78] NSABB defines this as "research in the life sciences that is directly and immediately applicable for hostile purposes," clearly a topic that all researchers should understand.

Continued improvements in DNA synthesis technology will lead to dramatic increases in the amount of DNA being synthesized and a rapid increase in the diversity of the educational backgrounds, professional disciplines, and types of technical expertise held by the users of the technology. Today many users of DNA synthesis technology are research professionals who work at well-funded commercial organizations (e.g., biotechnology and pharmaceutical companies). Many of these professionals lack access to continuing-education programs that could inform them about the social implications of synthetic genomics and its governance. Thus, early exposure at the college or university level to these concerns is critical for at least priming these workers to consider broader societal issues.

The annual student synthetic biology competition called iGEM (International Genetically Engineered Machine)[79] has been expanding participation rapidly. The 2006 event, the third one held, drew about 380 students from

Any laptop computer can be used to access public DNA sequence databases, place an order for DNA synthesis, and arrange for rapid delivery by overnight mail.

around the world. 700-800 have registered for the 2007 event. When surveyed in 2006, only about 1% of the participating students said that they were aware of the 1975 Asilomar Conference on recombinant DNA research, the reasons for the conference, and, most important, the research oversight framework that resulted.

Finally, it is worth re-emphasizing that the level of technical expertise required to use DNA synthesis technology is quite modest and getting lower. For example, any laptop computer can be used to access public DNA sequence databases on the Internet, download and use free software for editing DNA (including sophisticated protein design software), place an order for DNA synthesis on a website, and arrange for rapid delivery by overnight mail. Thus, it is naïve to expect that all well-intentioned users of DNA synthesis will have completed a degree program in biology, biological engineering, or a related field whose curriculum mandates some form of biosafety and biosecurity training. Moreover, for individuals whose education does provide such training, there is little opportunity to update this knowledge as technology and best practices evolve. Thus, as noted above, a professional society for synthetic biologists could play a key role in implementing these ongoing activities, as it would be the one institution that most workers in the field could have in common.

III-2. *Compilation and use of a manual for "Biosafety in Synthetic Biology Laboratories"*

Though several laboratory manuals and guides already exist for use by researchers and by the Institutional Biosafety Committees (IBCs) responsible for the safe conduct of research at their institutions, none are specifically designed for synthetic genomics. The National Institutes of Health (NIH) issues guidelines for the safe handling of recombinant DNA,[80] and the CDC and NIH together publish a handbook, ***Biosafety in Microbiological and Biomedical Laboratories*** (BMBL)[81] that covers general laboratory safety. Several clinical laboratory guides are available. Recently, the World Health Organization (WHO) published a guidance document on laboratory biosecurity to complement its existing manual on laboratory biosafety.[82]

All of these documents are clearly useful for work in synthetic genomics. However, there are a few defining aspects of this new research that the existing documents do not address now but will need to in the future. One major concern is with multi-source chimeras that are assembled from the DNA of hundreds of different organisms (in contrast to the up to tens of sources used by existing genetic engineering methods) as well as entirely novel synthetic constructs. In neither case is it known if, or to what degree, chimeras containing DNA from many different non-pathogenic sources could become pathogenic. The data on this topic are mostly anecdotal: experiments using recombinant DNA have been conducted for upwards of 30 years and to date there is no evidence of pathogens having been created from bona fide non-pathogenic precursors. At the same time, there has been little study of the emergence of pathogencity as a result of the recombination of pieces of nucleic acid. With respect to the design and construction of totally novel viral genomes, virtually no data exist indicating how one could make or avoid making a pathogen.

Thus, it would be helpful to develop a new compilation of biosafety guidelines for researchers working with a large number of aggregated synthetic genes, or with synthetic genomes. Certainly, the existing biosafety guidance could be modified to cover synthetic genomics and synthetic biology. However, given that synthetic genomics differs in several respects from current genetic engineering techniques, it would seem worthwhile to prepare a new biosafety manual, even if it incorporates large verbatim sections of the BMBL or any other existing set of guidelines.

A new biosafety manual for synthetic biology might be drafted at the CDC and NIH, which are already responsible for the current BMBL.

Other agencies might also want to be involved in drafting and updating such a document. Certainly, a non-governmental organization such as the American Biological Safety Association could make an important contribution to such a document, either independently or in collaboration with or under contract to the CDC. A professional society, particularly one dedicated specifically to synthetic biology, could also participate in or coordinate these efforts.

Irrespective of which agency leads such an effort, a critical component would be the need for active participation by current researchers and practitioners, and ongoing review and updating. As outlined in earlier sections of this report, the science of synthetic genomics is changing rapidly, and the social context of the research is changing rapidly as well. The current 5th edition of the BMBL follows the 4th edition that had been in use for over seven years, from 1999-2007. For a new manual titled "Biosafety in Synthetic Biology Laboratories" (BSBL) to be effective, it would have to be revised in response to new data in a timely manner.

A BSBL could also be a critical component for the institutional expert review of experimental protocols. A well-written biosafety manual (and the training that would accompany it) could address in one place safety problems that are generic to molecular biology and those specific to synthetic genomics and synthetic biology. Particularly if IBCs take on new or expanded responsibilities, supplying them with a manual that has everything in one place would seem to be a minimum contribution to ensuring best practices.

A laboratory biosafety manual for synthetic genomics would focus exclusively on minimizing the physical hazards associated with such experiments and would not address the issue of dangerous knowledge.

III-3. *Clearinghouse for best practices*

An on-line or telephone clearinghouse could be established as a centralized source for information on laboratory best practices for synthetic genomics. In addition, during an emergency, such a clearinghouse could provide information helpful to responders (see below) but it would not serve as a reporting hotline or as part of an emergency response.

Several clearinghouses for best practices exist in other fields and might serve as models for this option. For example, the National Fire Protection Association maintains a web site containing a comprehensive library of information and has a toll-free number for advice on technical questions.[83] The University of Chicago has a clearinghouse for scientists trying to find the answers to questions about regulatory compliance.[84] With respect to reporting and analysis, American Whitewater's safety program maintains an outstanding database on paddling accidents, including fatalities, and includes a vehicle for anyone to enter additional data.[85]

Regardless of how such a clearinghouse would be run, a key aspect is to allow people to share data on mistakes and accidents. Anonymous reporting should be possible, which would encourage submissions even from those who might fear criminal or civil sanctions if they were identified and who would otherwise not report. However, submissions would not have to be anonymous, and some researchers might even prefer to be identified so that they can explain to others the nuances of avoiding future mistakes or accidents.

A clearinghouse could be established by either a government agency or a professional society of synthetic biologists, should such a society be established.

III-4. *Broaden IBC review responsibilities to consider risky experiments*

The Fink Committee[86] recommended that Institutional Biosafety Committees become more attentive not just to the biosafety implications of certain areas of research involv-

A professional society for synthetic biologists could play a key role in implementing ongoing educational activities, as it would be the one institution that most workers in the field would have in common.

ing DNA ("dangerous research") but to the biosecurity risks associated with such research ("dangerous knowledge").

The Committee listed seven experiments of concern for biosecurity reasons: (1) demonstrating how to render a vaccine ineffective; (2) conferring resistance to therapeutically useful drugs; (3) enhancing the virulence of a pathogen or rendering a nonpathogen virulent; (4) increasing transmissibility; (5) altering host range; (6) enabling the evasion of a diagnostic or other detection; and (7) enabling weaponization.[87] While such experiments may strike investigators as extreme, they do happen under various guises. For example, many gene therapy experiments seek to develop viral vectors that can evade the human immune system. This characteristic is clearly related to the concern of enhancing the virulence of a pathogen, yet many investigators (and IBCs) may not think of it that way.

Anonymous reporting to a clearinghouse should be possible, but some researchers might prefer to be identified so that they can explain the nuances of avoiding future mistakes or accidents.

There is likely to be disagreement as to whether IBCs could or should handle the new task of assessing the security implications of dual-use research. The original purpose of the IBCs (specifically, to deal with recombinant DNA protocols) has been greatly expanded and problems have already been documented with IBCs failing to fully carry out their existing biosafety missions.[88] Assuming, however, that some oversight of security issues is a legitimate role for IBCs, it would then become the responsibility of the institutions (and by extension, the funders of research) to ensure that the committees are sufficiently staffed and educated (see III-5).

Although the initial product of synthetic genomics projects is a strand of DNA that is chemically indistinguishable from any other natural or recombinant DNA, synthetic genomics has raised new concerns with respect to laboratory and environmental safety. These concerns relate both to the process (Is there anything about working with synthetic DNA that is inherently different than working with natural DNA?) and the product (Are products made from synthetic DNA likely to be more dangerous than products made with genetic engineering?).

There are at least three different biosafety concerns with respect to the process and products of synthetic genomics in the laboratory. First, similar to the situation with traditional microbiology, there are concerns about working with specific, identifiable pathogens. Next are concerns about working with chimeras that combine genes from different organisms (specifically when large portions of the engineered product are derived from a pathogen). Finally, concern has been expressed about the possible emergence of pathogenicity from assembling pieces of DNA from dozens or even hundreds of different source organisms. If many pieces of non-pathogenic DNA are combined in ways that have never occurred in nature, could this process possibly give rise to something dangerous?

As the new field of synthetic genomics begins to expand rapidly, it would be desirable to have some type of formal process to identify and review experiments for both safety and security concerns. IBCs are a logical choice for such a task. Minimally, such a review would be for the seven specific types of experiments identified in the Fink Report, but local committees could decide to expand on this list. Indeed, the NSABB has released a draft guidance document for generically identifying dual-use research of concern that expands on the Fink criteria.[89]

III-5. *Broaden IBC review, plus oversight from a National Advisory Group to evaluate risky experiments*

Historically, review of recombinant DNA experiments and enforcement of biosafety rules have taken place at the local or institutional level. This approach has proven quite successful over time. Occasionally, however, a proposed experiment is so novel that the expertise available on the local IBC is not adequate to assess its risk, or the experiment may be controversial or difficult to assess for other

reasons. In such cases, the NIH's Recombinant DNA Advisory Committee (RAC) provides oversight of experiments that cannot be addressed by local IBCs. The best-known group of experiments subjected to such review is various gene therapy protocols.

A similar national oversight body might be established to review the biosafety of selected synthetic genomics experiments, for example, those involving the construction of chimeric microorganisms using DNA from many different organisms, an area where there is little precedent and hence a lack of local expertise. This review and oversight body might also be asked for biosecurity advice in cases where an experimental protocol has a clear potential for misuse for hostile purposes. Such a national review body could be housed in a number of agencies. It could be the RAC itself or the National Science Advisory Board for Biosecurity (NSABB) which, like the RAC, is operated by the NIH Office of Biotechnology Activities. Given the confluence of science and security responsibilities that such a review body would need to have, the NSABB, which is comprised of nongovernmental experts skilled in the science, safety, and security disciplines, could be a logical choice. However, that body was established in a purely advisory capacity with no operational responsibilities; assigning it the mission of reviewing and overseeing certain synthetic genomics experiments, or other issues that local IBCs could not resolve, would significantly change the Board's role.

Alternatively, a national oversight committee could be placed in a different agency within the Department of Health and Human Services (DHHS) such as the CDC, or it could be taken out of HHS entirely. In addition, such a body could be located outside of government. For example, it might be administered by a consortium of universities, with the voluntary participation of commercial biotechnology and pharmaceutical firms.

To make a national biosecurity oversight system more or less equivalent to the current RAC system, in which decision-making authority is vested in government officials to whom the RAC reports, there should be an additional level of review above any new national-level oversight body. In the case of the RAC, for example, the NIH director has final say on the approval of recombinant DNA research protocols. Given that any review process for synthetic genomics would have an important security component, the official to which the national body reports should have security as well as scientific responsibilities. This individual could still be the NIH director, or it could be a senior official with science and security responsibilities in another Executive Branch Agency.

It would be desirable to have some type of formal process to identify and review experiments for both safety and security concerns.

III-6. *Broader IBC review, plus enhanced enforcement of compliance with biosafety guidelines*

In addition to any penalties that institutions might levy against principal investigators who fail to comply with IBC rules, penalties can be levied against their institutions (usually universities). These institutional penalties range in severity, up to the revocation of NIH grants. Criminal penalties are a possibility as well, but they would typically not be invoked unless an individual was harmed. These most severe penalties are rare. Recently, the CDC issued a cease-and-desist order for work on Select Agents at Texas A&M University following multiple infractions that resulted in a worker becoming ill from a Brucella infection.[90]

Beyond the more or less voluntary nature of compliance with the NIH Guidelines, investigators and institutions are subject to legally binding regulations, including the Toxic Substances Control Act, the rules of the Nuclear Regulatory Commission, and the rules of the Occupational Safety and Health Administration, as well as tort liability. Our focus here is specifically on researchers following guidelines.

This option proposes that biosafety rules and guidance relevant to synthetic genomics, both those that already exist and new ones that may

A national oversight body might be established to review the biosafety of selected synthetic genomics experiments such as those involving the construction of microorganisms using DNA from many different organisms.

be developed, should to be strictly enforced. Moreover, the punitive measures provided for in the relevant Guidelines would be invoked whenever warranted, with the expectation that others will take compliance more seriously if they see cases in which noncompliance is punished.

This approach would represent a change in philosophy with respect to the oversight of science, which has typically relied on a presumption of good faith on the part of the research community, reserving punitive measures for particularly egregious cases. A more adversarial approach might require new types of oversight for these committees, or it may simply be the case that more committees are needed as responsibilities expand.

Comparing the Options

All of the options discussed above are aimed at legitimate researchers. Specifically, they address ***biosafety*** (the safety of laboratory workers and the surrounding communities, and protection of the environment) and mechanisms for achieving it. A few of the options also confer benefits for biosecurity. A summary table is found below in **Options Table III**.

Relative effectiveness for achieving goals

For ***fostering laboratory safety*** (specifically, the safety of workers) and ***protecting the surrounding communities and the environment,*** Option III-1, educating laboratory workers, is of great importance. This option involves teaching workers how to avoid laboratory accidents and what to do in case one occurs. The curriculum would involve both formal classroom teaching and practical training in the laboratory with an experienced researcher. The latter approach could be particularly effective because most training in laboratory best practices occurs on a one-on-one basis and is highly valued by students. In the event of an accidental release of a pathogen into the environment, prior education is likely to be less effective, as it will most likely only cover generalities.

Education could also have a positive impact on ***biosecurity*** particularly if the training program includes consideration of how biological research might be misused and how to anticipate and reduce that risk. Moreover, improved laboratory security as a result of such training could help to prevent would-be bioterrorists from obtaining dangerous biological materials by stealing them or using facilities to which they should not have access.

Option III-2, the development and use of a new biosafety manual for synthetic genomics, scores very high both for preventing biosafety incidents and helping to respond to an environmental release. In the latter case, the manual would contain step-by-step instructions for dealing with an accident. Equally effective in the event of an environmental release would be a telephone hotline to a good information clearinghouse that would provide explicit instructions (Option III-3).

Option III-4, broadening IBC review responsibilities to include the "experiments of concern" as defined by the Fink committee and the NSABB would have a modest impact on biosecurity. Combining the broadening of IBC review responsibilities with oversight by a National Advisory Group (Option III-5) would achieve a somewhat higher score for preventing a biosecurity incident. In both cases, however, the impact would be indirect. A review and oversight mechanism would not prevent specific incidents of bioterrorism but might result in the modification of dual-use experiments in a way that reduces their utility for potential bioterrorists. None of these options would help in responding to actual incidents.

Broadening IBC review is judged as moderately effective in preventing incidents that could harm either laboratory workers or nearby populations. We judge this option to be somewhat less effective in responding to incidents than education or the use of a manual. However, when combined with oversight by a national advisory group or with enhanced enforcement, the combinations are relatively

effective at preventing biosafety incidents. None of the options III-4, III-5, or III-6, alone or in any combination, is particularly effective for responding to incidents.

Relative effectiveness on other criteria

Although none of the options discussed above would require ***additional research*** per se, for many of the options, at least some additional information would be necessary. For example, for educating new entrants to the field, although there are no standard curricula, there are some examples of training programs for both the scientific and professional ethics aspects of research. For the use of a new manual, a BSBL does not yet exist, but other biosafety manuals with significant relevant information already do. The one area that would appear to require genuinely new research would be to address concerns over the construction of novel chimeras. Although, as discussed above, the possibility exists that a pathogen could emerge from the combination of otherwise benign pieces of DNA, there is little primary research on this topic.

Once these issues have been clarified, it is possible that the options discussed above could make a significant contribution to enhancing the biosafety in synthetic genomics research, but with varying impacts in other areas. These impacts could also depend on how the programs are implemented. For example, depending on who is chosen to run the clearinghouse, it could either ***minimize costs to government and industry*** (and universities) or increase costs. Establishing education programs and preparing a BSBL would require some initial financial investment on the part of government, academia, and perhaps industry. If implemented effectively, however, these biosafety measures should minimize overall operating costs in the long run. Moreover, if a professional society of synthetic biologists were established and assumed primary responsibility for developing these programs, they would entail essentially no costs to government or industry.

Two of the options are most effective for ***promoting the constructive applications of synthetic genomics***. These are Option III-1, education about risks and best practices, and Option III-3, a clearinghouse for best practices.

From the standpoint of the researcher or practitioner, virtually all of the review and oversight options would ***impede research*** to some extent. However, the availability of tools such as a BSBL or an information clearinghouse would not impede the advance of synthetic genomics and might even accelerate progress by suggesting better ways to carry out research protocols; a National Advisory Group might also facilitate research by offering "gold standard" advice that could be difficult to come by at the local level.

Additional Concerns

Thinking past the U.S. border

Laboratory best practices, while to some degree culture-specific, tend to spread internationally through spontaneous adoption as well as efforts of the community. The American Biological Safety Association, for example, has endeavored to include the laws and practices of other countries in its training materials,[xi] and biosafety meetings, regardless of the country they are held in, draw international attendees.[xii] Formal curricula in schools and universities can be exported to other countries and informal education occurs at international meetings, through collaborators, etc. Thus, the options concerning education and biosafety (Options III-1, 2, and 3) could not only be implemented internationally but potentially could have positive impacts on the conduct of research by influencing the behavior of scientists and engineers throughout the world.

Improved laboratory security as a result of good training could help to prevent would-be bioterrorists from obtaining dangerous biological materials by stealing them.

[xi] See, e.g., http://www.absa.org/resguides.html
[xii] See, e.g., http://www.absa50.org/program.html

Options Table III: Summary of Options for Users and Organizations

Does the Option:	III-1. Education about risks and best practices in university curricula	III-2. Compile a manual for "Biosafety in Synthetic Biology/ Laboratories"	III-3. Establish a clearinghouse for best practices	III-4. Broaden Institutional Biosafety Committee review responsibilities	III-5. Broader IBC Review, plus oversight by National Advisory Group	III-6. Broaden IBC review, plus enhanced enforcement
Enhance Biosecurity						
by preventing incidents?	○	—	—	○	◎	○
by helping to respond?	○	—	—	—	—	—
Foster Laboratory Safety						
by preventing incidents?	◎	●	○	○	◎	◎
by helping to respond?	◎	—	—	○	—	—
Protect the Environment						
by preventing incidents?	◎	●	○	○	◎	◎
by helping to respond?	○	◎	◎	○	—	—
Other Considerations:						
Minimize costs and burdens to government and industry?	◎	○	○	○	○	○
Perform to potential without additional research?	◎	○	○	○	○	◎
Not impede research?	●	◎	●	○	◎	○
Promote constructive applications?	●	◌	○	○	—	—

Key to Scoring:

- ● Most effective for this goal. Most effective performance on this consideration.
- ◎ Relatively effective.
- ○ Moderately effective.
- ○ Somewhat effective.
- ◌ Minimally effective.
- — Not relevant.

Options III-4, III-5, and III-6, however, are more difficult to harmonize internationally. Institutional biosafety committees and national-level advisory groups tend to focus on local or domestic concerns. Certainly, other countries beside the United States could propose parallel oversight mechanisms, and they could work to harmonize their respective procedures for biosafety and biosecurity reviews of proposed experiments. However, it would be difficult to tie these national procedures together into a single international system.

Keeping pace with evolving science and technology

Option III-3, an information clearinghouse, and to a lesser extent, Option III-2, a laboratory manual for synthetic biology, are two good ways to help the community stay abreast of the biosafety implications of this rapidly changing technology. Given appropriate support, both of these measures can be updated and used in real-time to deal with emerging safety issues (and to some degree, security concerns). Option III-1, education, will of course deal with these sorts of changes as well, though somewhat more slowly as curricula are adjusted over time.

IBCs and other groups concerned with the oversight of research do their best to take into account the latest scientific findings in making their decisions. Such changes may at times occur slowly. On balance, however, oversight bodies are probably more effective at responding to a fluid research environment than are individual scientists. To keep pace with changing science and technology, Option III-5, which includes a national oversight body, would likely be more effective than Option III-4, which places such burdens on local IBCs alone.

Mitigating risk by review prior to publication

One issue that those involved in prior review of experiments will likely have to wrestle with is concern about the publication of experimental results and genetic sequences that could be exploited for malicious purposes. For several years, the scientific community has been considering whether and how restrictions on communication of sensitive research findings might be an appropriate response to the potential misuse of the biological sciences and of biotechnology. Our study does not present policy options for controlling information that go beyond what is being discussed among the scientific and security communities more broadly. We believe that ongoing discussions and policy options proposed by others, which are described below, adequately address the risks, benefits, and practical difficulties of synthetic genomics.

In February 2003, the editors of several prestigious scientific journals issued a statement reiterating the importance of open scientific communication in research and technology development, but acknowledging that "there is information that, although we cannot now capture it with lists or definitions, presents enough risk of use by terrorists that it should not be published."[91] The group went on to conclude that "on occasion, an editor may conclude that the potential harm of publication outweighs the potential societal benefits. Under such circumstances, the paper should be modified, or not be published."[92] Drafters of this statement did not give government a role in making this determination, but rather assigned this responsibility to editors, publishers, and the researchers themselves.

This idea was carried forward in the Fink Committee, which in its October 2003 report recommended "relying on self-governance by scientists and scientific journals to review publications for their potential national security risks."[93] The committee's recommendation endorsed the statement from the editors and publishers group but did not provide guidance for what to do with information that may be excluded from publication. The Fink Committee did, however, reject the creation of a new category of "sensitive but unclassified" information in the life sciences, stating that the risks

"of a chilling effect on biodefense research vital to U.S. national security as the result of inevitably general and vague categories is at present significantly greater than the risks posed by inadvertent publication of potentially dangerous results."

The NSABB, formed a subgroup on communications to pursue the issue. This subgroup recognized that the communication of scientific research involves several stages other than formal publication of final results. Reiterating the importance of open and unfettered sharing of information and technologies for validating and advancing scientific research, the subgroup went on to consider how to assess the risks and benefits of communicating research information. The subgroup formulated options for the content, timing, distribution, and/or context of research information that poses security concerns.[94] Given the diversity of communication mechanisms, the subgroup recognized that to the extent a line of research can be anticipated to raise questions about future dissemination of results, it would be preferable to address those questions at the proposal stage. Questions involving proposal review and research oversight are being addressed in a separate NSABB subgroup

Of particular relevance to synthetic genomics, a workshop was held at the National Academies in October 2003 to address concerns about the potential for misuse of genome sequence data and to examine policies governing access to databases containing those data. Its report argued against any kind of monitoring of or restrictions to access, concluding that "rapid, unrestricted public access to primary genome sequence data, annotations of genome data, genome databases, and Internet-based tools for genome analysis should be encouraged."[95] Since naturally-occurring pathogens represent ongoing public health threats, any restrictions on the ability to understand and counter them would have serious consequences. However, this finding was motivated as much by the practical difficulties in limiting access to genome data as by the judgment that such limitations would be undesirable.

In the longer run, however, scientific communication may rely less and less on "gatekeepers" such as peer reviewers, editors, and publishers. In the future, it is possible that scientific communication will evolve from a formal system based on pre-publication review to an informal, "Wikipedia" type mechanism in which results are circulated worldwide immediately and are then reviewed and vetted after the fact. Such a trend would place sole responsibility for what to communicate on the individual scientist..

Choosing a portfolio of options

Options Table IV includes our evaluations of all 17 options proposed in the previous sections. The challenge that faces decisionmakers is to choose a portfolio of options that will achieve the multiple goals desired.

The top half of the table includes our judgment of how relatively effective each option is for achieving the three key goals of enhancing biosecurity, fostering laboratory safety, and protecting the environment. Increasing the number of options adopted will likely enhance the Nation's ability to achieve these goals, but no option is without drawbacks.

The bottom half of the Table includes rankings of how well these options perform on four additional important considerations: What costs and other burdens do they impose on government and industry? Can they perform to potential today or do they require additional research? Will they unduly impede progress in synthetic biology and other related research? Finally, do the options help to promote constructive applications, rather than just prevent undesirable ones?

Although we have provided our best judgments about the broad benefits and costs of each of these options, our ability to do so is extremely limited in some cases. For example, while we have pointed out that synthetic genomics would rarely be the preferred method for a bioterrorist to acquire a pathogen, we have no way of judging the overall likelihood of such an event. Thus, we can only judge the *rela-*

Options Table IV: Summary of All Options

Does the Option:	Gene Firms								Oligo Manufacturers			DNA Synthesizers	Users and Organizations					
	IA-1. Gene firms must screen orders	IA-2. Biosafety officers must certify people who place orders	IA-3. Hybrid: Firms must screen and biosafety officer must verify people	IA-4. Firms must store information about orders	IB-1. Oligonucleoside manufacturers must screen orders	IB-2. Biosafety officer must verify people who place orders	IB-3. Hybrid: Firms must screen and biosafety officer must verify people	IB-4. Firms must store information about orders	II-1. Owners of DNA synthesizers must register their machines	II-2. Owners of DNA synthesizers must be licensed	II-3. Licensing of equipment, plus license required to buy reagents and services	III-1. Education about risks and best practices in university curricula	III-2. Compile a manual for "Biosafety in Synthetic Biology Laboratories"	III-3. Establish a clearinghouse for best practices	III-4. Broaden IBC review responsibilities	III-5. Broaden IBC review, plus oversight by National Advisory	III-6. Broaden IBC review, plus enhanced enforcement
Enhance Biosecurity																		
by preventing incidents?	◉	○	●	○	○	○	◉	○	◌	○	○	○	–	–	○	○	○	
by helping to respond?	–	–	–	○	–	–	–	○	◌	◌	◌	○	–	–	–	–	–	
Foster Laboratory Safety																		
by preventing incidents?	○	–	○	–	◌	–	◌	–	–	–	–	◉	●	○	○	◉	◉	
by helping to respond?	–	–	–	–	–	–	–	–	–	–	–	◉	–	–	–	○	–	
Protect the Environment																		
by preventing incidents?	○	–	○	–	–	–	–	–	–	–	–	◉	●	○	○	◉	◉	
by helping to respond?	–	–	–	○	–	–	–	○	–	–	–	○	◉	◉	○	–	–	
Other Considerations:																		
Minimize costs and burdens to government and industry?	○	○	○	●	○	○	○	●	●	◉	○	◉	○	○	○	○	○	
Perform to potential without additional research?	○	●	◉	○	○	●	○	○	●	●	◉	◉	○	○	○	○	◉	
Not impede research?	◉	◉	○	●	○	○	○	●	◉	○	○	●	◉	●	○	◉	○	
Promote constructive applications?	–	–	–	–	–	–	–	–	–	–	–	●	○	○	○	–	–	

Key to Scoring:

- ● Most effective for this goal. Most effective performance on this consideration.
- ◉ Relatively effective.
- ○ Moderately effective.
- ○ Somewhat effective.
- ◌ Minimally effective.
- – Not relevant.

tive effectiveness of the options for enhancing biosecurity; that is, how each option compares to the others. Quantitative estimates of the added security provided by each option are simply not possible.

Similarly, we can estimate the *relative* effect each option may have on the progress of the field of synthetic genomics, but we are not able to take this analysis much further. While we believe that the potential of the technology is high, we have no crystal ball that can tell us the future of the field with and without any of the policy options.

When making decisions about the governance of synthetic genomics, policymakers will bring their own values, priorities, prior beliefs, and extent of risk aversion regarding safety and security threats to their analyses and decisions. They will also emphasize different goals and other considerations, leading to varying assessments of the desirability of each of the policy options. To help each decisionmaker choose a preferred set of options, we have constructed several portfolios ranging from a modest set of controls on the new technology to one that is quite aggressive.

Table 4 presents the mix of options within each of three illustrative scenarios. The options are again arranged by "intervention point;" that is, whether they apply to gene- or genome synthesis companies, manufacturers of oligonucleotides, laboratory-benchtop DNA synthesizers, or the users of the technology and the organizations in which they work. Note that we can construct many groupings that would use slightly different options, with slightly different outcomes. These three portfolios are presented as examples only.

The first portfolio is aimed at plugging the biggest holes in the current system of governance for synthetic genomics. The options included are those that we judge to provide the greatest benefits at the lowest costs and burdens. The second and subsequent portfolios add options to enhance biosecurity and biosafety, but the relative "bang for the buck"—the added benefit compared to the undesired impacts—of these added options will be lower than those in the preceding portfolios. Each successive portfolio strikes a different balance between concern for the potential harm that might arise from synthetic genomics versus the desire to preserve its benefits and to avoid imposing other costs on society.

Decisionmakers will differ in their preferred balances. In addition, perceptions of the optimal balance will change over time as more is learned about the risks and benefits of synthetic genomics. Thus, the flexibility of the overall portfolio is another important consideration. Decisionmakers should expect that the program they adopt today will need to be reconsidered in several years' time.

Again, the first portfolio includes those options that provide the greatest benefit at the lowest cost and burden. For example, the first option listed in Table 2, *Gene synthesis companies must screen orders,* is already being done voluntarily by the majority of gene synthesis companies. This option is aimed simply at the relatively small fraction (perhaps 25%) of U.S. firms that do not. The next two options, requiring both *Gene synthesis companies and oligo manufactures to store information,* is also being done today by many U.S. firms for business and regulatory reasons. The goal of these options is to ensure that all firms store their orders and that the FBI would be able to access such records in the event that a bioterrorism incident involving a synthesized genome should occur.

Education about the risks and best practices, is already occurring in some university curricula, but not many. Accordingly, this option is directed at the majority of students and researchers new to the field who have not had rigorous biosafety training or have not had the opportunity to think through the potential societal impacts out of their research. Finally, the development and use of a *Biosafety manual developed explicitly for synthetic biology laboratories* (a "BSBL") would make such information easily accessible to this expanding community of scientists and engineers.

Table 4: Summary of Portfolios

Intervention Point	Option	Portfolio 1	2	3
Gene Foundries	IA-1. Require commercial firms to use approved software for screening orders	●		
	IA-2. People who order synthetic DNA from commercial firms must be verified as legitimate users by an Institutional Biosafety Officer or similar "responsible official"			
	IA-3. Commercial firms are required to use approved screening software and to ensure that people who place orders are verified as legitimate users by a Biosafety Officer		●	●
	IA-4. Require commercial firms to store information about customers and their orders	●	●	●
Oligo Manufacturers	IB-1. Require commercial firms to use approved software for screening orders			
	IB-2. People who order synthetic DNA from commercial firms must be verified as legitimate users by an Institutional Biosafety Officer or similar "responsible official"		●	
	IB-3. Commercial firms are required to use approved screening software and to ensure that people who place orders are verified as legitimate users by a Biosafety Officer			●
	IB-4. Require commercial firms to store information about customers and their orders	●	●	●
DNA Synthesizers	II-1. Owners of DNA synthesizers must register their machines			
	II-2. Owners of DNA synthesizers must be licensed		●	
	II-3. A license is required to both own DNA synthesizers and to buy reagents and services			●
Users and Organizations	III-1. Incorporate education about risks and best practices as part of university curricula	●	●	●
	III-2. Compile a manual for "biosafety in synthetic biology laboratories."	●	●	●
	III-3. Establish a clearinghouse for best practices			●
	III-4. Broaden Institutional Biosafety Committee (IBC) review responsibilities to consider risky experiments		●	●
	III-5. Broaden IBC review responsibilities and add oversight from a national advisory group to evaluate risky experiments		●	●
	III-6. Broaden IBC review responsibilities, plus enhance enforcement of compliance with National Institutes of Health biosafety guidelines			●

The second portfolio adds several more options to the mix. Again, the added benefits of these options compared to the undesired impacts, are lower than in the first portfolio. Some decisionmakers will judge these options to be useful additions while others may choose to forgo them.

For example, the second portfolio adds an additional option for both gene synthesis companies and oligo manufacturers: *Orders can only be placed by legitimate researchers, as verified by a registered biosafety professional.* As in the first portfolio, gene synthesis companies must still screen their orders, but because of the lower effectiveness and increased burden of screening short pieces of DNA as compared to genes, oligo manufacturers are not required to do so. Oligo manufacturers are, however, required to ensure that orders come from legitimate researchers.

The second portfolio also includes *Licensing of DNA synthesizers.* Though synthesizing a pathogen with only a laboratory synthesizer and the necessary reagents requires additional time and skills, it is nonetheless possible.

Organizations would be required to shoulder a new burden by *Broadening local institutional review of proposed research involving DNA synthesis* to include implications for bioterrorism. *National level reviews* for bioterrorism and biosafety could be introduced here to deal with issues that are not covered in a BSBL.

The options in the third portfolio begin to address concerns about biosecurity and biosafety that might never be encountered by most legitimate users, or that may be considered to be unduly burdensome. This portfolio requires the *Licensing of synthesizers plus licensing to buy reagents and services rather than licensing of synthesizers alone. A Requirement for oligo houses to screen their orders* (under the hybrid option) is introduced here, as its technical feasibility remains unclear. A *Clearinghouse* would be added to augment many of the topics included in a BSBL. Finally, *Enhanced enforcement of biosafety guidelines* is included to increase the effectiveness of either current or expanded IBC reviews.

Appendices

I. Core Group Members

The Core Group for this study consisted of 18 individuals with a wide range of expertise, and included scientific and engineering researchers; social scientists; and legal, regulatory, and policy analysts.

Ralph Baric, University of North Carolina

George Church, Harvard Medical School

Drew Endy, Massachusetts Institute of Technology (project co-director)

Gerald L. Epstein, Center for Strategic & International Studies (project co-director)

Robert M. Friedman, J. Craig Venter Institute (project co-director)

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Michele S. Garfinkel, J. Craig Venter Institute (project co-director)

Tom Knight, Massachusetts Institute of Technology

Lori Knowles, University of Alberta

John Mulligan, Blue Heron Biotechnology

Paula Olsiewski, Alfred P. Sloan Foundation (project program officer)

Tara O'Toole, University of Pittsburgh Medical Center, Center for Biosecurity

George Poste, Arizona State University Biodesign Center

Michael Rodemeyer, Pew Initiative on Food and Biotechnology

Susanna Hornig Priest, University of Nevada, Las Vegas (formerly at University of South Carolina)

Hamilton Smith, J. Craig Venter Institute

Jonathan B. Tucker, Monterey Institute of International Studies

J. Craig Venter, J. Craig Venter Institute

II. Commissioned Papers

Baric R. 2006. *Synthetic Viral Genomics.*

Collett M. 2006. *Impact of Synthetic Genomics on the Threat of Bioterrorism with Viral Agents.*

Fleming D. 2006. *Risk Assessment of Synthetic Genomics: A Biosafety and Biosecurity Perspective.*

Furger F. 2006. *From Genetically Modified Organisms to Synthetic Biology: Legislation in the European Union, in Six Member Countries and Switzerland.*

Jones R. 2005. *Sequence Screening.*

Sanghvi Y. 2005. *A Roadmap to the Assembly of Synthetic DNA from Raw Materials.*

III. Meetings Held

Workshops

26-27 September 2005. Cambridge, Massachusetts. *Technologies for Synthetic Genomics.*

27-28 February 2006. Rockville, Maryland. *Risks and Benefits from Synthetic Genomics.*

31 May-1 June 2006. Washington, District of Columbia. *Governance Options.*

Invitational Meeting

4 December 2006. Washington, District of Columbia. *Synthetic Genomics: Risks and Benefits for Science and Society.*

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Institute Information

The J. Craig Venter Institute (JCVI) is a not-for-profit research institute dedicated to the advancement of the science of genomics; the understanding of its implications for society; and communication of those results to the scientific community, the public, and policymakers. Founded by J. Craig Venter, Ph.D., the JCVI is home to approximately 500 scientists and staff with expertise in human and evolutionary biology, genetics, bioinformatics/informatics, information technology, high-throughput DNA sequencing, genomic and environmental policy research, and public education in science and science policy. The legacy organizations of the JCVI are the Institute for Genomic Research, the Center for the Advancement of Genomics, the Institute for Biological Energy Alternatives, the Joint Technology Center, and the J. Craig Venter Science Foundation. The JCVI is a 501 (c)(3) organization.

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