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Preventing the Misuse of DNA Synthesis

Five policy recommendations to curb downside risk

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Introduction

Scientific advances have made it cheaper and easier than ever to produce synthetic DNA. Synthetic DNA is now fundamental to much life sciences research and is likely to contribute to important advances in medicine and other important uses of biological sciences.

However, like other powerful tools, synthetic DNA also has the potential to cause harm, whether by accident or intention. Experts in global health and biosecurity have warned that synthetic biology could be misused to cause a catastrophic pandemic far worse than COVID-19. One key reason for concern is the potential release of pathogens: it is possible to synthesize a viral genome and boot it up to be a living virus. This has been done for several dangerous viruses, including the influenza strain that caused the 1918 pandemic, and horsepox, a close relative of smallpox. Well-meaning scientists may cause an accidental release of a dangerous pathogen, while malicious actors may intentionally do the same.

The synthetic DNA industry has long been aware of the risk its product poses, and many companies have voluntarily implemented a screening system to mitigate this risk. Synthetic DNA providers verify customers' identities and monitor orders to ensure sequences that could cause harm aren't released inappropriately. However, screening is inconsistent across the industry, and as costs of DNA synthesis fall, screening will make up a greater proportion of companies' costs, making it harder for companies that perform screening to remain competitive with those who don't.

Rather than relying on the goodwill of industry to mitigate these threats, the United States (US) Government should proactively protect American citizens from the risks of synthetic biology. The US is a global leader in synthetic biology, accounting for roughly 40% of the global market. This puts the US in a powerful position to set industry standards. Market dominance enables the US to take leadership that should prompt action in other countries with growing synthetic biology industries.

In this report we review existing approaches to DNA synthesis screening, contemporary challenges, possible avenues for improvement, and strategic considerations. We then present five policy recommendations for the federal government which aim to reduce the risk of synthetic DNA while protecting the American biotechnology industry.

Past DNA synthesis screening

In 2006, as part of an investigation into practices in the synthetic biology industry, journalists from British newspaper *The Guardian* ordered a piece of smallpox DNA to a residential address. The ease with which they did this generated significant controversy. Prior to this incident, the synthetic biology community had discussed how to reduce the risk of dangerous DNA sequences being sold inappropriately. But this incident may have contributed to governments and industry taking action towards screening systems.

The following year, the National Science Advisory Board for Biosecurity (NSABB) delivered a report entitled Addressing Biosecurity Concerns Related to the Synthesis of Select Agents. The report made several recommendations for policy change, including the development of screening infrastructure that could be used by providers and users of synthetic DNA. It was followed by coordinated industry action in the establishment of the International Gene Synthesis Consortium in 2009, and the release of guidance on DNA synthesis screening by the Department of Health and Human Services (HHS) in 2010.

International Gene Synthesis Consortium

The International Gene Synthesis Consortium (IGSC) was established in 2009 to “safeguard biosecurity, apply a common protocol for screening DNA sequences and customers while promoting the beneficial use of gene synthesis.” Since its founding, the IGSC has come to include roughly 80% of the industry and actively recruits new members. Its members are required to follow its protocol for screening, which includes a Regulated Pathogen Database against which member companies screen the double-stranded DNA sequence orders they receive. The IGSC is discussed in more detail below.

The protocol recommends a homology or “best match” approach to screening. This involves comparing the ordered sequence to a publicly available database of known sequences and identifying which of these sequences is the closest match. If the closest match is a sequence associated with a harmful pathogen, then the order is flagged for further review by bioinformatics experts within the company.

2010 Department of Health and Human Services Guidance

In 2010, HHS released the Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA. The framework recommends a screening system composed of three main components: customer screening, sequence screening and follow-up screening. It notes

that screening is voluntary, but that the recommendations serve to remind providers of their obligations under existing regulations, including the Select Agent Regulations and the Export Administration Regulations.

The Select Agent Regulations govern the possession, use and transfer of the 68 pathogens and toxins on the Federal Select Agent Program (FSAP) list. This program is co-managed by the US Department of Agriculture (USDA) and the Centers for Disease Control and Prevention (CDC). It inspects entities that possess, use, or transfer select agents, and ensures that all individuals who work with select agents undergo a security risk assessment performed by the Federal Bureau of Investigation (FBI) and investigates possible incidents of non-compliance.

The Export Administration Regulations regulate the export of items on the Commerce Control List (CCL), including bacteria, viruses, toxins and fungi on the Australia Group List of Human and Animal Pathogens and Toxins for Export Control. They are enforced by an arm of the US Department of Commerce.

The HHS guidance recommends that providers screen all customers who place an order for synthetic DNA to verify their identity, ensure they are not on a list of denied or blocked persons and entities maintained by the Departments of Commerce, State, and Treasury, and assess for any "red flags." Suggested red flags include difficulty verifying the identity of a customer, the lack of a clear, legitimate need for the requested synthetic DNA, requests for unusual labeling or shipping procedures, requests to deliver to a private address or change the name on the order after it has been placed, unusual payment methods or willingness to pay a very high price, or unusual requests for confidentiality.

The guidance recommends screening sequences of double-stranded DNA to identify a *sequence of concern* (SOC). SOCs are double-stranded DNA sequences derived from or encoding Select Agents and Toxins and (for international orders) items on the CCL list. The guidance recommends providers use the best match approach for order screening. Software is available to assist with this screening process. For example, the National Center for Biotechnology Information has a family of tools, known as BLAST, which compare sequences to the NCBI database of pathogens and toxins and assess the best match. Commercial software is also available, such as ThreatSeq, licensed by Battelle, which encompasses both the alignment software and a database of SOC.

If customer screening or sequence screening raise any concerns, follow-up screening aims to determine whether the order should be filled. This may include ascertaining the intended use of the order, cross-matching with previous published research of the end user, and, where applicable, discussion with biological safety officers or other representatives from the institute associated with the order. The guidance recommends that providers contact the Federal Bureau of Intelligence (FBI) Weapons of Mass Destruction Coordinator if assistance is needed with making this determination.

New challenges since 2010 Guidance

In the years since the initial HHS guidance was released, the synthetic biology industry has changed significantly, creating new challenges. First, the cost of synthesizing DNA has fallen dramatically, leading to screening making up a substantially higher proportion of providers' costs. This makes it harder for providers who screen to compete with those who don't, creating a disincentive to screen. Second, new techniques have made it easier to combine smaller DNA fragments into larger sequences. This means that smaller orders that aren't screened (below the 200 base pair length recommended by the 2010 guidance for screening) could be more easily combined to create a SOC. Third, benchtop synthesizers have advanced and will likely become more common in the coming years. These machines could allow users to print whatever DNA sequences they like, avoiding the need for screening. Finally, advances in artificial intelligence applied to the life sciences may soon enable the capacity to generate novel sequences that confer pathogenic potential. Existing screening, based on matching sequences to known SOCs, would not detect such novel SOCs.

2022 Proposed Guidance Revision

In April 2022, HHS released a draft update to the guidance and made a public call for comments. The draft changes address many, but not all, of the challenges outlined above.

Its key proposed changes are:

- Recommending screening of sequences of synthetic DNA or RNA that are 50 nucleotides or greater in length, regardless of whether they are single-stranded or double-stranded.
- Recommending screening of batch orders of oligonucleotides.
- Updating the definition of sequences of concern to include sequences that contribute to toxicity or pathogenicity, whether derived from or encoding regulated or unregulated biological agents (in addition to SOCs derived from or encoding select agents and toxins or items on the CCL).
- Expanding the guidance to include third-party vendors, institutions, principal users and end users of synthetic oligonucleotides.
- Introducing guidance for manufacturers of benchtop DNA synthesis machines, who are advised to screen customers, track the legitimacy of users of their equipment, enable secure internet connectivity to screen requests for SOCs and to authenticate users, and keep a record of oligonucleotides synthesized.

HHS has requested comments on the proposed revisions. Several groups in the industry have made public comments outlining areas of agreement and disagreement, including the American Society of Gene and Cell Therapy (ASGCT), the Engineering Biology Research Consortium (EBRC), and the Nuclear Threat Initiative (NTI), writing in conjunction with the World Economic Forum (WEF). Each of these groups welcomed the expansion of the guidance to apply to third-party providers and screening for benchtop DNA synthesizers.

Persistent challenges

Although the proposed guidance revisions address some of the major challenges associated with DNA synthesis screening, many persist. The guidance does little to address the rising costs of conducting screening, and may even increase these costs with suggestions for more stringent screening.

Another major challenge is making screening compatible with the international nature of the synthetic DNA industry. Although US companies account for a significant portion of the market, there are many major international providers, and more will likely arise as countries develop their bioeconomies. Synthetic DNA customers are also distributed internationally. Conducting screening on international customers can be complicated due to differences in local requirements and research governance processes. An ideal screening system would also avoid hamstringing market competition by posing companies with varying regulatory environments.

Moreover, the field of synthetic biology continues to advance rapidly, and screening approaches will need to be sufficiently flexible and foresighted to keep up. New pathogens are being discovered, so any screening approach that compares orders to pathogens from known sequences requires regular updates to include new knowledge. It will also be important to consider non-pathogenic harms that could occur from synthetic DNA, such as the risk of novel methods for developing substances that are functionally similar to illicit drugs. The development of synthetic nucleotides (new base pairs, beyond the natural building blocks of DNA; G, T, C, and A) will also expand the number of small variations in SOCs that could retain the harmful function of the sequence.

Another important technological change is the development of benchtop synthesizers, which are becoming cheaper and more readily available. What's more, the development of AI models like DeepMind's Alphafold may soon enable the design of de novo sequences that could confer pathogenicity. Maintaining security in synthetic DNA screening will ultimately require a paradigm shift in the screening process; away from a homology-based approach and towards an approach based on sequence function. This may prove a major technical challenge that requires significant computational resources.

Proposals for improving screening

Several proposals have been made to improve DNA synthesis screening. They can be broadly categorized as either facilitating the screening process, or modifying the incentive structure for providers to conduct screening.

Facilitating sequence screening

Producing free-to-use software that facilitates sequence screening

NTI-WEF Common Mechanism

In 2019, NTI's Biosecurity Innovation and Risk Reduction Initiative, alongside members of industry and the WEF, began the process of creating a Common Mechanism to Prevent Illicit Gene Synthesis. The proposed solution to prevent misuse is "A common, globally accessible, and regularly updated mechanism to screen nucleic acid synthesis orders and customers." While few details on the specific details of this mechanism are public, the availability of a globally accessible, nominally neutral, and regularly updated screening system that removes some of the expense of screening from companies' balance sheets would placate some of industry's concerns.

In our conversations about the implementation of the Common Mechanism, the question of oversight came up regularly: who is approving the screening process? The ability of screening to keep up with rapidly advancing technology like improved benchtop synthesizers was also noted as a potential issue. The quality of data that is being used to screen must also be ensured, a considerable investment. One company was reportedly funding a data cleanup for the Common Mechanism but it is unclear how effective this will be and how frequently it will be maintained.

That said, the Common Mechanism is a very promising platform for screening. In addition to serving as neutral arbiter, it sets an important, norm-building precedent in the industry and can provide the foundation for any national legislation requiring screening.

SecureDNA

Another multinational group, SecureDNA, is developing a system that allows fully-automated, encrypted order screening. Rather than taking a homology-based approach, this system compares ordered sequences to specific sequences of pathogen genomes. This includes all relevant windows of a hazardous pathogen sequence, and millions of functional variants of specific subsequences. When combined with information from biosafety authorities on individuals and entities that have approval to work with hazardous sequences, this system could allow automated screening without the need for human review. In principle, this could allow screening to be conducted without cost to providers. This software is now available to several IGSC members and will soon be free to all synthetic DNA providers.

The current version of SecureDNA screens for publicly known hazards, but the group is investigating the possibility of expanding screening to include emerging hazards. To reduce the risk of hazardous information being accessed by bad actors, the details of emerging hazards would not be publicly accessible. Customers and providers would not be told why a sequence was flagged if screening identified it as a match to an emerging hazard. Some synthetic DNA providers have suggested this approach would complicate communication with customers whose orders were flagged.

The approach taken by SecureDNA has many benefits, including the potential for fully automated screening, which would significantly reduce (and possibly eliminate) costs to providers. Its use of encryption should also assure customers of synthetic DNA of the confidentiality of their orders. As noted earlier, SecureDNA overcomes the challenge of a malicious actor evading screening by ordering sequence fragments from several providers. A provider noted the significant technical challenge of determining the scope of the sequence or "hash" database such that all variations of sequences that retain function are included, but false positives are avoided. However, the SecureDNA team is confident their approach will detect all sequence variations that preserve function, while keeping false positives at a very low level. Providers also noted that while SecureDNA seemed promising, there is need for additional communication with industry on the project's benefits and capabilities. To enable a fully automated system, SecureDNA needs to integrate approvals from biosafety authorities across the world. This highlights the need for national governments to cooperate with international efforts by providing details of these approvals and helping the SecureDNA team to create a system that meets local standards.

Facilitating customer screening

Customer licensing

Customer screening – both routine and in response to flagged orders – comprises a significant proportion of the time required for screening. Staff at companies providing synthetic DNA must manually search for information on customers to determine whether they are a legitimate user of the product. For customers based outside the US, this can be particularly difficult. A system that requires companies to procure a license from a government agency – which conducts the necessary checks to determine if the customer should be considered a legitimate user of DNA – would substantially simplify the task of providers.

However, the international nature of the synthetic DNA industry would complicate a licensing system. It's unclear if international customers would be willing to pursue the process of registering with the US Government for a license. This may be a requirement that would simply push customers to find alternative providers, outside the US. This would not only harm the US biotechnology industry, but may not reduce risk if international providers do not participate in screening.

Developing better customer screening tools

Customer screening forms a significant portion of the costs of screening for providers. Software such as Bridger Insight allows companies to check prospective customers' names against the US Government's watch lists for terrorists, people engaged in trafficking weapons of mass destruction, and other lists that preclude an individual or entity from purchasing synthetic DNA products. However, apart from this initial screen, providers report there is little available to assist with assessing the legitimacy of a customer and their requests.

An alternative way to facilitate customer screening would be through the provision of guidance or other tools that speed up and simplify the process of verifying the legitimacy of customers. This could include the active management of a database of relevant research institutions and researchers, with information on their biosafety measures.

Linking screening to automatic reporting to authorities

One way to reduce the burden of screening to providers is to remove the need for follow-up screening and the need to make a judgment on whether or not to fulfill an order. A possible mechanism could be having all flagged orders sent to a central law enforcement agency (such as the FBI) which would monitor and conduct further investigation if the pattern of flagged orders suggested suspicious activity. As well as reducing the burden on providers, this proposal would allow the intelligence agency to combine intelligence sources, rather than relying on information on synthetic DNA requests alone.

There are several challenges for this approach. First, many customers may not be willing to have their data sent to a US Government intelligence agency. This may be particularly true for international customers, but may also be true for US-based customers, who may be wary of sharing information with the US Government due to previous incidents where work with biological materials led to legal difficulties despite no illegal activity. Many customers may also be wary of sending details of their orders to a third party due to concerns about compromised cybersecurity revealing proprietary information. Additionally, the FBI, as a law enforcement agency, would not be in a legal position to collect and screen data for transactions in which no suspected crime has taken place. Because of this, the repository would likely need to be the US Department of Health and Human Services and/or one of its operational divisions like the CDC, Food and Drug Administration (FDA), or the Administration for Strategic Preparedness and Response (ASPR), who would then pass on orders of concern to law enforcement.

These concerns could be partially alleviated by sending limited information to authorities, for example, the ordered sequence that resulted in the flag, but not the details of the customer requesting the sequence. Authorities could then request further information, such as whether multiple orders came from the same customer, to determine whether to arrange a warrant to gain the details of the customer from the provider. In any of these scenarios, procuring the necessary funding and legal structure would prove to be significant obstacles.

Modifying incentive structures

Regulation can be used to incentivize conducting screening or disincentivize not conducting screening.

Both approaches would require a way to determine whether companies are adequately screening. This would firstly require a definition of adequate screening, and a mechanism of assessing compliance with this standard. Membership in IGSC could be a proxy, but it's unclear if this would be a sufficient test of ongoing compliance. An alternative would be to assess a provider's screening methods against a standardized approach like the Common Mechanism.

Requiring federally funded research to use providers who screen

One way to incentivize compliance would be to require that US Government-funded research use synthetic DNA from providers. Given the major role that US Government funding plays in global scientific research, companies would have a strong incentive to be eligible to take orders from customers receiving this funding.

This idea was suggested by the NSABB in 2006, and has been raised several times since. In 2022, legislation in California implemented a version of this proposal by requiring the California State University system "develop systemwide guidance for purchasing gene synthesis equipment or gene synthesis products from gene synthesis providers who prevent the misuse of synthetic genes and safeguard the benefits of gene synthesis technology while minimizing risk."

This language was the watered down result of an earlier version that would have required the state Department of Public Health "to develop a process, with input from the IGSC and industry stakeholders, to verify that gene synthesis providers and manufacturers of gene synthesis equipment adhere to customer and sequence screening protocols that are equivalent to, or stronger than, the IGSC's Harmonized Screening Protocol." This bill passed both houses of the California legislature but was vetoed by Governor Newsom, reportedly out of fears of preemption by federal law.

Mandating screening

Finally, actions could be taken to enforce DNA synthesis screening. For example, if screening was to be mandated and managed by the government, the Federal Select Agent Program is one model that could be followed or indeed reformed to include a broader list of sequences of concern. There is some debate regarding whether the existing regulatory language could include some sequences of concern, however HHS does not seem to think that is the case. Because of this, enforcing broader screening, i.e. for sequences of concern that aren't related to pathogens on the FSAP or CCL lists, would likely require legislative change or addition of all potential pandemic pathogens to the FSAP.

A legal requirement to conduct screening would increase screening rates amongst US providers, and could help to shift international norms in the synthetic DNA industry. However, there are fears that regulation in the US would cause customers to move to international providers who are not required to screen.

Industry perspective

Industry primarily engages with the screening conversation through the IGSC. The IGSC's current stated goal is "to design and apply a common protocol to screen both the sequences of synthetic gene orders and the customers who place them." According to its website, the IGSC also "works with national and international government organizations and other interested parties to promote the beneficial application of gene synthesis technology while safeguarding biosecurity."

The commonly quoted statistic, by the IGSC and others, is that 80% of DNA synthesis orders are screened. While we have seen no hard evidence to support this number, it is a reasonable conclusion, considering the IGSC represents the 10 largest synthetic DNA companies.

The synthetic biology industry seems altruistically and institutionally motivated to screen. Synthetic biology professionals tend to understand the power of the technology they work with and its associated dangers. Institutionally, no company wants to be responsible for allowing a bad actor to access a dangerous sequence.

Industry leaders are funding improvements to the IGSC's screening mechanism. For example, Batelle is reportedly funding an update to the IGSC database. Additionally, IGSC members are participating in the NTI-WEF Common Mechanism and the alpha test of SecureDNA. This cooperation seemingly arises from the fact that customer and sequence screening are expensive and time consuming. An industry representative noted that at least one company has a team of PhD-level staff reviewing flagged orders, allegedly adding more than 1% to their bottom line. GeneWiz, a large provider which is being recruited by the IGSC, has thus far resisted joining because its margins are too small and the expense of building and staffing a screening protocol is prohibitive. GeneWiz is, however, interested in participating in the Common Mechanism.

Participation in tests of the Common Mechanism and SecureDNA is likely a response to industry's motivations to screen. From an institutional/financial perspective, allowing a neutral organization to build a cooperative screening system will dilute the costs for any individual company to the point where it becomes economically viable, even for companies with lower profit margins.

Industry leaders have closely followed the development and pending trials of SecureDNA. There is particular interest in the cryptographic screening of customers, which would address the heaviest cost burden that companies carry, as well as the privacy concerns that could arise from a government registry (described below). There is some skepticism around whether a comprehensive database of sequences could be built, but this poses a problem for all screening approaches.

Recommendations

It appears to us that leaders in the synthetic DNA industry generally agree on the risks associated with their products. This understanding has brought a willingness to proactively engage in developing screening mechanisms, in particular NTI's Common Mechanism but also the SecureDNA project at MIT. Any legislative action taken should work to support this norm and look to integrate the tools they have developed. Most importantly, it should not attempt to replace these efforts with a system that could interfere with innovation, undermine US industry leadership, or create what one interviewee called "security theater."

We make the following recommendations:

1. As a matter of urgency, introduce legal requirements for the manufacture and sale of benchtop DNA synthesizers.

In recent years benchtop DNA synthesizers have started coming to market, and as this technology develops, it is likely these machines will become more accessible. Without regulation, benchtop synthesizers could allow screening systems to be bypassed, allowing any sufficiently skilled individual to print dangerous DNA sequences without detection. Regulation of these tools early in their usage would limit their potential harm and establish an important norm that recognizes the danger that they pose.

Regulations should require that:

- Benchtop synthesizers are only sold to entities that have a legitimate reason to synthesize DNA, have adequate biosafety and biosecurity training and facilities, and are not on any security watchlists;
- Before printing, machines compare all requested sequences against a database of sequences of concern, which is promptly updated as new hazardous sequences are identified;
- Potentially hazardous sequences are only synthesized for users who have authorization to work with the sequence;
- Machines require authentication of individual users;
- There are strict penalties for sale of machines without these safeguards and for the unauthorized synthesis of hazardous sequences.

The Federal Select Agent Regulations govern the possession, use and transfer of a list of pathogens that pose a threat to human and animal health. Without the interventions recommended above, manufacturers of benchtop synthesizers may not abide by these regulations. As new hazardous sequences are discovered, regulations may need to be updated to include them.

2. Introduce a legal requirement for providers of synthetic DNA to conduct screening of customers and orders, or if this is met with considerable opposition, require that research funded by the US Government strictly use synthetic DNA from providers that participate in screening.

Unless all companies conduct screening, it will not be difficult for a motivated actor to access harmful DNA sequences. Therefore, a legal requirement for all companies to conduct screening to an agreed-upon standard is the best pathway to minimize risks from synthetic DNA. New tools, such as the Common Mechanism and SecureDNA, promise to remove many of the financial and operational barriers to screening, such that it is accessible even to small providers. Many industries are regulated to ensure public safety and the risks from synthetic DNA are now high enough to warrant regulation.

The US has a long history as international leaders in technology regulation. The US showing leadership on this issue may prompt other countries to follow suit, especially as international initiatives to promote and facilitate screening become established.

If a legal mandate is politically infeasible, an alternative would be requiring all research funded by the US Government to use providers that meet a minimum screening standard. The US Government is a major funder of life sciences research and synthetic DNA companies have a strong incentive to ensure that they can supply this large share of the market with their product. This requirement would result in many companies ensuring that they reach the required standard of screening. While this requirement is unlikely to result in universal screening, it will help to generate norms of screening and pave the way for wider regulations in the future should these be considered necessary. This could also be paired with a Buy American clause that would have a similar impact.

Either version of this legislation would develop a screening standard and a system for verifying compliance with that standard. Ideally this standard would be consistent with or integrate international standards, such as the NTI-WEF Common Mechanism. At a minimum this standard should include screening for pathogens on the Federal Select Agent Program (FSAP) list and the CCL. However, as understanding of hazardous DNA sequences develops, the requirements should expand to include this new knowledge. Enforcement could sit solely within HHS, specifically the newly formed ASPR, which has been managing the recent updating of HHS's gene synthesis guidelines.

One course that should be explored further is whether legislation is necessary to enact this regulation, or if HHS could institute this policy under its current authority. This may be possible without legislation via HHS's regulatory authority and/or executive action. It may be at the agency's discretion on how and to whom previously allocated funds are disbursed.

3. Investigate mechanisms to facilitate the process of customer screening.

The time and resources spent to investigate prospective customers and flagged orders are a major component of screening costs to providers, and likely create a major barrier to smaller companies deciding whether to screen. We recommend working with industry partners to investigate options for facilitating this process, to alleviate some of the financial burden associated with screening.

Options may include a licensing program or centralized database where prospective customers would register their details, including information on research, publications, biosafety at their facility, and link this to approvals to work with certain pathogens (e.g. FSAP). This system should be developed in a manner that protects the privacy of those using synthetic DNA. This could also be linked to government watch lists to create a simple and fast way for providers to gain the necessary information to make a decision about whether or not to fill a flagged order.

4. Support international efforts to develop screening processes, and in engage with other countries with major synthetic biology industries.

As the synthetic DNA industry is international, the US must engage with and support efforts to promote screening. This includes collaborating with international initiatives that aim to simplify and standardize screening, including the International Gene Synthesis Consortium and the International Biosecurity and Biosafety Initiative for Science. HHS has significant expertise in developing safe screening protocols. By sharing this expertise, HHS can help to develop international screening guidelines that meet US standards and create international consistency in screening. Consistent international screening standards will reduce risks, promote international trade, and minimize the risk of US industry being harmed by inconsistent regulation, all while building an important norm of safety in this field.

Similarly, international groups developing automated screening systems, such as the Nuclear Threat Initiative and SecureDNA, may need the cooperation of governments to incorporate approvals to work with certain pathogens into these automated systems. HHS (which oversees the FSAP) and the Department of Commerce (which oversees the CCL) should cooperate with these groups to enable the efficient development of these systems.

It is important to recognize that all countries, particularly those with advanced synthetic DNA industries, have an interest in reducing risks from the technology. Diplomatic engagement with other nations that host major synthetic gene industries will be vital in building a global regulatory structure that encourages safe scientific advancement.

5. Investigate options to adapt screening processes to the changing technology landscape.

The field of synthetic biology will evolve substantially in the coming years. Current screening approaches use DNA sequences from known pathogens and toxins. Knowledge of these pathogens is evolving so all screening systems will need to be updated promptly. However, more importantly, application of artificial intelligence to the life sciences may soon allow the design of de novo DNA sequences that have the potential to cause harm. This will require a new approach to DNA synthesis screening. The US Government should investigate how to address this coming challenge to current screening approaches.

However, it is important that any government efforts not contribute to these risks by advancing functional prediction capacities. Rather than funding research into sequence functional prediction, the government should work with relevant companies and researchers (those whose models may enable de novo prediction) to reduce these risks. The optimal action would be best developed in partnership with companies and relevant researchers, but may involve restricting access to models that could be used to generate dangerous de novo sequences, and/or ensuring that these companies and researchers are working with groups producing synthetic DNA screening platforms (such as the Common Mechanism and SecureDNA) to develop mechanisms to screen for dangerous sequences that may be generated by models.

Conclusion

The synthetic biology industry has potential to bring enormous benefits, but also carries the risk of accidental or intentional harm. Given the power of this technology, this harm could be substantial and potentially catastrophic. The synthetic DNA industry has been proactive in establishing systems for self-regulation. However, with screening making up a greater portion of company costs, it is no longer appropriate to rely on the goodwill of private companies to guard against this substantial risk to the American public.

The five recommendations made here will reduce risks from synthetic DNA while maintaining the central role of industry in regulation. Given the risks posed by synthetic DNA and the development of tools to facilitate the screening process, we believe a legal requirement to conduct screening is warranted. This requirement should be combined with efforts to facilitate screening processes, ensure that screening adapts to changes in technology, and is coordinated with international efforts. The US has long been a leader in biotechnology and should continue that leadership in creating global norms that will allow the bioeconomy to grow safely.