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Insight Report

Biosecurity Innovation and Risk Reduction: A Global Framework for Accessible, Safe and Secure DNA Synthesis

In collaboration with the Nuclear Threat Initiative (NTI)

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Contents

World Economic Forum
91-93 route de la Capite
CH-1223 Cologny/Geneva
Switzerland
Tel.: +41 (0)22 869 1212
Fax: +41 (0)22 786 2744
Email: contact@weforum.org
www.weforum.org

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Preface

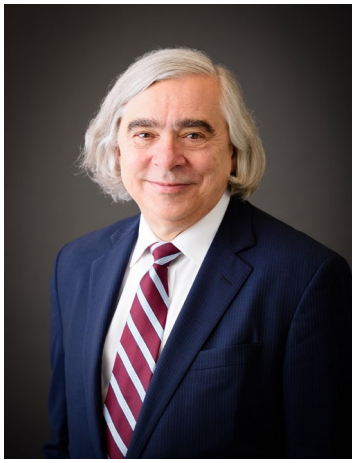
Arnaud Bernaert
Head of Shaping the Future of Health and Healthcare
World Economic Forum

The Fourth Industrial Revolution describes a world where new technologies and approaches are merging the physical, digital and biological worlds in ways that stand to transform society. Ensuring that this transformation is positive will depend on how the risks and opportunities that arise along the way are navigated.

Biotechnology is at the centre of the Fourth Industrial Revolution. To deliver on the promise of the biotechnology revolution, we must seize opportunities to develop and deliver life-advancing innovations while simultaneously and urgently addressing potential risks associated with a growing and democratized bioeconomy. Throughout the process of developing its recommendations, the Working Group recalled that the internet was built without cybersecurity in mind. The same choice now lies before us, at the beginning of the biotechnology revolution.

It is a credit to the Working Group that, as the biotechnology revolution is creating undreamed-of possibilities for innovation and industrialization, due consideration is given to managing risk so that the chance to build the biotechnology revolution with biosecurity in mind is not missed.

Foreword



Ernest J. Moniz
Chief Executive Officer
Nuclear Threat Initiative
(NTI), USA

As a scientist and former government official with responsibility for the United States' nuclear stockpile, I am acutely aware of both the promise and peril of technological advances. That's why, after leaving government service in January 2017 and joining the Nuclear Threat Initiative (NTI) to focus on nuclear and biological dangers, one of the first areas I prioritized was the intersection of technology and the risks posed by weapons of mass destruction.

When it comes to rapid advances in biotechnology, there is a double-edged sword. New innovations hold the promise of a future that is more resilient to disease, food insecurity and environmental instability, and there is no doubt that advances in genomics, synthetic biology and microbiology will continue to prove essential for a safer, healthier and more secure future for all. At the same time, advances in technology, including cheaper DNA synthesis and widespread access to gene editing tools, have made it possible for a broader array of actors to manipulate biological agents and systems. Together, the innovations and access portend an increase in the risk of a potentially catastrophic biological event, whether deliberate or accidental.

It is vital that leaders – technical and policy – understand these risks and have the tools to mitigate them. Unfortunately, we are behind on this front. Today, there is no expert organization or body to provide recommendations and guidance on reducing the biological risks associated with these and future technology advances. With this need in mind, NTI convened the Biosecurity Innovation and Risk Reduction Initiative to bring together global technical experts, international organizations, companies, investors, researchers and their institutions, funders, publishers and insurers to catalyse the adoption of new approaches to reduce biological risks associated with advances in technology.

We view DNA synthesis screening as one effective tool to reduce the risk that life science technologies could be deliberately misused to carry out biological attacks or could accidentally result in a high-consequence or catastrophic biological event. Unfortunately, no governments currently require screening for DNA synthesis, and developing, implementing and maintaining screening procedures are becoming increasingly expensive relative to other business costs. This creates an economic disincentive for companies to do the right thing. Potentially compounding the problem is that benchtop DNA synthesis is now within reach, posing significant additional challenges that the international scientific community and global decision-makers have yet to fully imagine.

It is time for the commercial sector to standardize the uneven patchwork of security and safety practices across facilities, countries and regions, but the screening mechanism described in this report is only a start. A larger system of common global life science norms must be established in parallel and will require oversight from a globally recognized normative entity. NTI and the World Economic Forum are dedicated to convening senior leaders from governments, companies and international organizations to plan its creation.

Collectively, we can realize the promise of biotechnology while simultaneously reducing and, wherever possible, eliminating associated catastrophic risks. The time is now.

Introduction

In 2002, scientists demonstrated the *de novo* synthesis of a full viral genome. Since then, DNA synthesis technologies capable of printing pathogen or toxin DNA have become widely available via a relatively small number of companies and other DNA providers. At the same time, synthesized DNA has become a staple of life sciences research and biotechnology development, and this DNA's availability has become critical for technological and economic advances.

As access expands and the cost of DNA synthesis declines, more DNA will be in commerce and additional DNA providers may enter the market, further expanding the range of people using synthetic DNA. Although many DNA providers practice screening procedures to help prevent the misuse of synthetic DNA, these practices are becoming increasingly expensive relative to other business costs, thus increasing economic pressure to limit such procedures. Many of these providers have expressed a desire for shared assurance of reliable screening across the industry. In addition, in the next two to three years, a new generation of benchtop DNA synthesis machines, enabled by enzymatic DNA synthesis methods, will become available without guidance or norms to prevent misuse. Within a decade, these machines could significantly expand the availability of synthetic DNA around the world. In this context, it is increasingly critical to safeguard against the misuse of DNA synthesis technologies to make pathogen or toxin DNA (see Appendix B for additional details), either intentionally by malicious actors or unintentionally by other users. **Now is the time to act to establish a more global approach to prevent deliberate or accidental misuse of DNA synthesis technologies.**

In 2019, the Nuclear Threat Initiative and the World Economic Forum organized an international expert Working Group on Preventing Illicit Gene Synthesis to develop the basis for a durable, global norm to prevent the misuse of synthetic DNA and for a possible mechanism that could facilitate the implementation of such norms. This report, issued with the Working Group's concurrence, summarizes its findings and makes a set of urgent recommendations for further action.

Executive summary

To mitigate the risk of deliberate or accidental misuse of pathogen or toxin DNA, some policy-makers and companies have developed frameworks for screening DNA synthesis orders and customers. In 2010, the United States published guidance for providers of synthetic double-stranded DNA to screen both customers and the DNA sequences ordered. Since then, members of the International Gene Synthesis Consortium (IGSC), established in 2009, developed a harmonized screening protocol that could be implemented by individual companies to guard against the delivery of double-stranded DNA encoding pathogenic processes or toxins to nefarious actors and others without a legitimate use for those sequences. These voluntary practices are implemented and funded internally by individual companies that decide to adopt them and are not universally followed in the DNA synthesis industry. Screening practices at companies that are not members of the IGSC – a notable fraction of the total DNA synthesis market – are largely unknown and may fall below established best practice.[1]

Barriers to voluntary synthetic DNA screening practices among DNA synthesis companies are growing as well. First, significant time and expertise are required to determine which ordered DNA sequences require additional scrutiny and to follow up with customers who ordered those sequences. These costs place smaller DNA providers and those in developing markets at a disadvantage. Furthermore, as new DNA sequences are discovered at an ever-increasing rate, computational costs for sequence screening also increase. At the same time, the price of DNA synthesis is declining, which makes the portion of corporate costs associated with synthetic DNA screening a more significant portion of the overall profit margin for companies performing this service. This creates a financial disincentive for screening within the entire industry; therefore, current DNA providers may increasingly struggle to maintain screening practices in the near future, and new companies may decide to forgo screening practices altogether. In addition, the imminent arrival of a new generation of benchtop DNA synthesis machines could further challenge current DNA screening practices, as no established expectations and best practices exist to prevent misuse of the machines to synthesize pathogen or toxin DNA. The world urgently needs a new mechanism for expanding synthetic DNA screening practices.

The NTI-Forum Working Group was comprised of policy experts, leading industrial providers of gene synthesis and academic experts (listed in Appendix A). NTI and the Forum also solicited input from additional key stakeholders throughout the process. The recommendations (see Box 1) were developed with the Working Group's concurrence; they describe a system to globally expand synthetic DNA screening practices by developing an international, cost-effective and sustainable common mechanism to prevent illicit DNA synthesis and misuse. The mechanism will reduce the economic burden on DNA providers to adopt screening practices and create solutions for providers of benchtop DNA synthesis machines to also adopt these procedures. These recommendations build on international experiences to date with synthetic DNA screening practices; they extend and expand beyond the current voluntary system towards a broader set of solutions.

> **"The Working Group believes that the proposed common mechanism will reduce the risk of deliberate or accidental misuse as access to synthetic DNA and the tools of synthetic biology rapidly expands to a wider range of actors."**

The proposed common mechanism should be considered as a critical tool among a broader set of approaches to prevent misuse of advanced biotechnologies. Such a mechanism is unlikely to reduce DNA synthesis risks from some sophisticated actors, including those with significant resources and/or scientific training, such as state actors. Even so, the Working Group believes that the proposed common mechanism will reduce the risk of deliberate or accidental misuse as access to synthetic DNA and the tools of synthetic biology rapidly expands to a wider range of actors. Moreover, the institutions described and recommended here will serve to support the development of global norms for safeguarding against the misuse of DNA synthesis technologies to make pathogen or toxin DNA, highlight the importance of this issue internationally and serve as a focal point for understanding the challenge. Perhaps most importantly, it will serve as a foundational structure for instituting more effective mechanisms that can be built over time as the science and technology evolve.

1 Cision PR Newswire, "International Gene Synthesis Consortium Updates Screening Protocols for Synthetic DNA Products and Services", 3 January 2018, https://www.prnewswire.com/news-releases/international-gene-synthesis-consortium-updates-screening-protocols-for-synthetic-dna-products-and-services-300576867.html

Box 1: Recommendations

Developing a Common DNA Sequence Screening Mechanism

1) By early 2020, establish a global, standing, multistakeholder, technical consortium ("the Consortium") to develop a common DNA sequence screening mechanism that is accessible at low cost, secure and easy to use by all providers of DNA and providers of benchtop DNA synthesis machines. This mechanism would include an internationally recognized set of sequences of pathogen and toxin DNA (see Appendix B for additional details) and algorithms to screen ordered DNA sequences against that set of sequences. The Consortium should work to develop a version of the screening mechanism that is fully automated for ease of use and integration as a built-in feature of benchtop DNA synthesis machines.

2) As the common DNA sequence screening mechanism is developed, the Consortium should consider security precautions and built-in technical safeguards to prevent its misuse.

3) By 2021, the common DNA sequence screening mechanism should be supplied to all DNA providers to incorporate into their operations. Regular updates should be established thereafter.

4) By 2021, the common DNA sequence screening mechanism and its updates should be supplied to all developers and providers of benchtop DNA synthesis machines to incorporate into their machines and/or operations.

   a. The Consortium should work with providers of benchtop machines to implement procedures to screen each DNA sequence before it is synthesized.

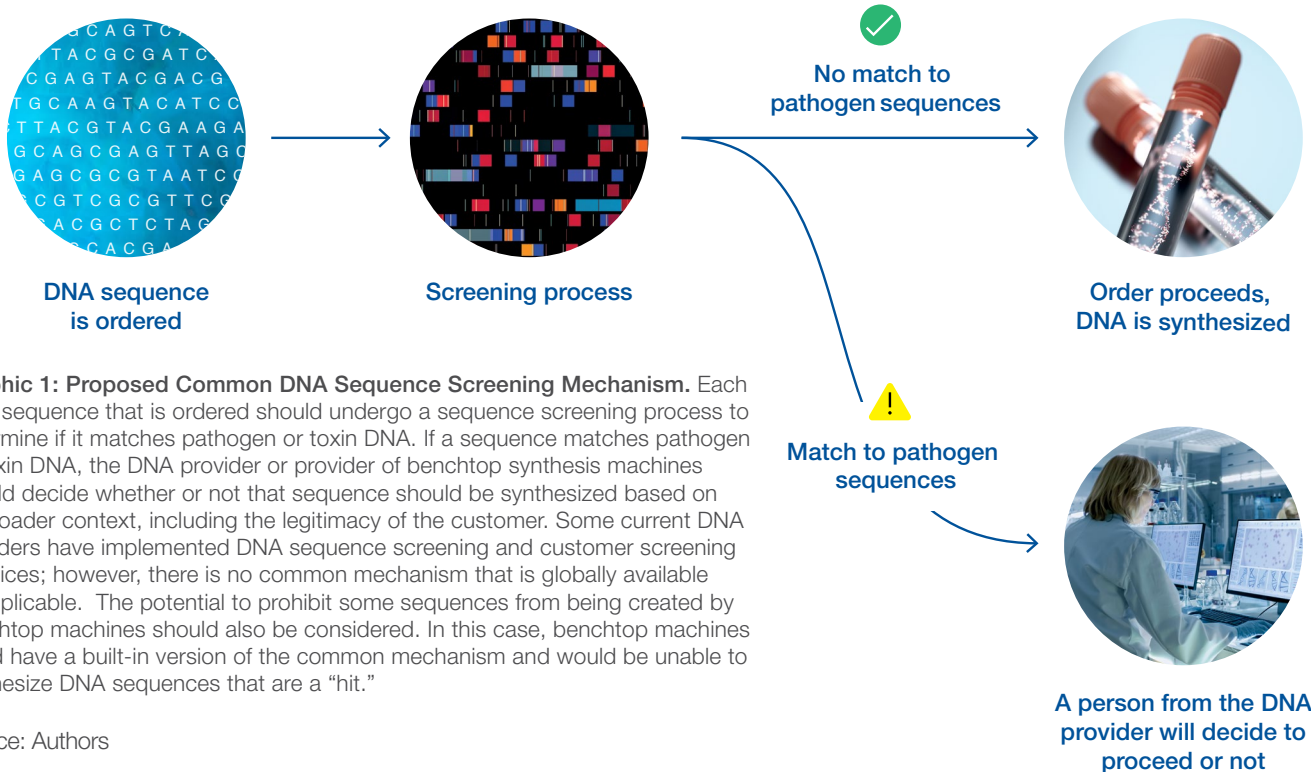
   b. The Consortium should consider the potential to prohibit some sequences from being created by benchtop machines. In this case, benchtop machines could have a built-in version of the common mechanism and would be unable to synthesize DNA sequences that are a hit.

Oversight, policies and partnerships for establishing synthetic DNA screening as a global norm

1) The Consortium should be funded as an independent technical entity for at least two years so that it can immediately start work to meet the goal of developing the common DNA sequence screening mechanism and providing it to DNA providers and providers of benchtop DNA synthesis machines by 2021.

2) In early-to-mid 2020, NTI and the World Economic Forum should convene senior leaders from governments, companies and international organizations to explore options for the sustainable oversight of the Consortium and maintenance of the proposed DNA sequence screening mechanism. These options may include developing synthetic DNA screening as a new mandate for an existing international entity or the creation of a new organization to take on this mandate.

3) In partnership with the new or existing organization focusing on this work, the technical Consortium should work with states, international organizations, industry groups, universities and others to pursue opportunities to strengthen synthetic DNA screening as a global norm and standard among governments, researchers, institutions, and providers of DNA and benchtop DNA synthesis machines.



Graphic 1: Proposed Common DNA Sequence Screening Mechanism. Each DNA sequence that is ordered should undergo a sequence screening process to determine if it matches pathogen or toxin DNA. If a sequence matches pathogen or toxin DNA, the DNA provider or provider of benchtop synthesis machines should decide whether or not that sequence should be synthesized based on its broader context, including the legitimacy of the customer. Some current DNA providers have implemented DNA sequence screening and customer screening practices; however, there is no common mechanism that is globally available or applicable. The potential to prohibit some sequences from being created by benchtop machines should also be considered. In this case, benchtop machines could have a built-in version of the common mechanism and would be unable to synthesize DNA sequences that are a "hit."

Source: Authors

Developing a common DNA sequence screening mechanism

Recommendation 1

By early 2020, establish a global, standing, multistakeholder, technical consortium ("the Consortium") to develop a common DNA sequence screening mechanism that is accessible at low cost, secure and easy to use by all providers of DNA and providers of benchtop DNA synthesis machines. This mechanism would include an internationally recognized set of sequences of pathogen and toxin DNA and algorithms to screen ordered DNA sequences against that set of sequences. The Consortium should work to develop a version of the screening mechanism that is fully automated for ease of use and integration as a built-in feature of benchtop DNA synthesis machines.

DNA synthesis providers have strong incentives to ensure that their products are not misused, whether deliberately or accidentally. Development of a common mechanism for screening pathogen and toxin DNA would reduce the time and expertise required to adopt and implement synthetic DNA screening practices, and thereby expand those practices to a wider range of DNA providers. The companies of the International Gene Synthesis Consortium (IGSC) have developed a database of sequences of concern that each company adapts to its needs, but no broadly recognized screening mechanism exists for this purpose (i.e. list of DNA sequences to screen against and algorithms to conduct the search). Furthermore, there has been very little development of technical approaches that could be used in a more automated way or incorporated into the workflow of benchtop DNA synthesis machines.

As a first step, the Consortium should generate international, expert consensus on a set of publicly available DNA sequences most likely to cause harm when misused. These sequences would likely include those most clearly linked to pathogens and toxins identified as being particularly harmful. Many of these DNA sequences are already considered to be controlled under regulatory and export regimes, such as the Australia Group, EU Regulation No 428/2009 and the US Select Agents Regulations, which provide some legal basis for synthetic DNA screening practices in many countries. Along with the set of consensus DNA sequences, the common mechanism would include screening algorithms that would give all DNA providers and providers of benchtop DNA synthesis machines the capability to input an ordered DNA sequence and return a "hit" when that sequence matches a sequence in the common set of DNA sequences (see Appendix B). This mechanism would have to be fast and computationally scalable to efficiently accommodate a volume of DNA orders that may increase by orders of magnitude over the next several years. It would also be updated on a regular basis to include new sequences (or to remove sequences) as scientific understanding of how DNA sequences endow or enhance pathogenicity or confer other types of risks evolves, and to incorporate improvements in synthetic DNA screening practices. Appendix C includes some of the considerations for the mechanism that are likely to arise in the near future and potential directions the Consortium could consider.

The Consortium should serve as the international focal point for synthetic DNA screening, related tools and best practices. It is essential that it be transparent in its processes and membership, globally representative, engaged with the DNA synthesis industry and have dedicated funding. See Box 2 for the Consortium's specific tasks.

Box 2: Tasks for the Consortium

The Consortium will be an international focal point for synthetic DNA screening, including the development of the common DNA sequence screening mechanism. Because promulgation of synthetic DNA screening practices as a global norm will first require a functional common DNA sequence screening mechanism, the Consortium should establish its mandate and schedule of activities as soon as possible. The Consortium should be tasked with:

- Providing the common mechanism to DNA providers by 2021. This will include convening industry and governmental experts as soon as possible to determine work plans for parallel development of the consensus set of sequences of pathogen and toxin DNA and computationally scalable screening algorithms.

- Holding small, focused technical meetings to advise on pathogenicity, determination of non-pathogen risks from emerging synthetic biology, new ways to screen DNA sequences, best practices for screening customers, and the potential to create built-in approaches to secure and prevent benchtop DNA synthesis machines from making unauthorized pathogen or toxin DNA.

- Meeting semi-annually to update the common mechanism to incorporate new scientific findings as well as technological and algorithmic advances into the common screening mechanism as science advances, new information is learned and computing capabilities improve.

- Collecting and acting as a repository for resources and information related to the common set of sequences and screening platform, including regulations and guidance related to synthetic DNA and best practices for DNA sequence screening and customer screening.regulations and guidance related to synthetic DNA and best practices for DNA sequence screening and customer screening.

Recommendation 2

As the common DNA sequence screening mechanism is developed, the Consortium should consider security precautions and built-in technical safeguards to prevent its misuse.

It is possible that a common screening mechanism of this type could create "information hazards" by, for example, inadvertently enabling nefarious actors by highlighting DNA sequences most likely to contribute to pathogenicity and by increasing understanding of synthetic DNA screening practices. These concerns should be addressed in the common mechanism, and precautions should be taken to mitigate any specific risks identified. Furthermore, the organization implementing the mechanism should adopt a process to consistently review the effectiveness of these precautions and to identify new risks and potential mitigation measures over time. The Consortium might initially consider a wide range of approaches to ensure that the security benefits of the common DNA sequence screening mechanism outweigh any security risks that may arise as a consequence of the mechanism. A few of those approaches and considerations are listed below. As the Consortium weighs these issues, it should also consider that it will need to maintain a level of transparency in the development and testing of the common mechanism to guarantee trust and legitimacy among its international participants and partners.

Restrict access: The Consortium should consider restricting access to the common DNA sequence screening mechanism and taking additional measures to safeguard its contents. As the Consortium develops the common mechanism and makes it available, care should be taken to verify that it is housed securely and only available in an encrypted form. The Consortium should also consider alternative mechanisms to limit access to the sequences included in the mechanism, including novel methods of encryption or use of secure cloud-based systems. These measures should be balanced with the need for DNA providers and providers of benchtop DNA synthesis machines to have easy access and to make use of the common mechanism, and the need to share the common mechanism with outside experts to review its completeness, correctness and security, both during the mechanism's development and in an ongoing way.

Limit the mechanism to publicly available sequences and data: The Consortium could limit what is included in the common set of sequences to those that are publicly available, thereby limiting the potential for information hazards. Full genome sequences of the most harmful known pathogens, including those most likely to generate international consensus for inclusion in the common set of sequences, are already widely available. In the future, as more is understood about how DNA sequences (and their biological functions) endow or enhance pathogenicity, the Consortium could continue to incorporate publicly available scientific advances. Such an approach would significantly limit the possibility that a nefarious actor could discover novel means of endowing or enhancing pathogenicity through the common mechanism.

Secure the decentralized system: Related to the question of security is how centralized or decentralized the common DNA sequence screening mechanism should be. Today, a centralized system, whereby DNA providers from around the world send customer sequences to a central location for screening, is not feasible due to data security and privacy (particularly for DNA synthesis companies) and to the lack of a universally trusted entity to house the common mechanism. A fully centralized mechanism could also pose a security risk if hackers or others sought to tamper with the system. The Consortium should consider the security implications of a more decentralized system and work to mitigate identified risks and vulnerabilities.

Recommendation 3

By 2021, the common DNA sequence screening mechanism should be supplied to all DNA providers to incorporate into their operations. Regular updates should be established thereafter.

As a first step, the common screening mechanism would be supplied to all DNA providers (see Appendix B for definitions), which would immediately expand screening capabilities to companies and providers that are not members of the IGSC and may have limited in-house DNA sequence screening expertise. If the common mechanism returns a hit for an ordered DNA sequence, the DNA provider will know it matches pathogen or toxin DNA in the consensus set of sequences at a level requiring manual evaluation. For DNA providers that choose not to synthesize pathogen or toxin DNA, this system could be fully automated, with a hit conveying a decision that synthesis should not proceed.

If a DNA provider chooses to synthesize pathogen or toxin DNA (i.e. sequences that are a hit in the common mechanism), the provider would have to determine that it will be used for legitimate purposes. To make such a determination, the provider would need more information about the DNA sequence that was ordered (e.g. what type of gene and from which organism), and would need to conduct follow-up screening of the customer to verify that the end user of that DNA has a legitimate use for it.

Recommendation 4

By 2021, the common DNA sequence screening mechanism and its updates should be supplied to all developers and providers of benchtop DNA synthesis machines to incorporate into their machines and/or operations.

a. The Consortium should work with providers of benchtop machines to implement procedures to screen each DNA sequence before it is synthesized.

b. The Consortium should consider the potential to prohibit some sequences from being created by benchtop machines. In this case, benchtop machines could have a built-in version of the common mechanism and would be unable to synthesize DNA sequences that are a hit.

This recommendation is based on the current synthetic DNA screening practices by current DNA providers, and includes the same requirement that pathogen or toxin DNA (i.e. sequences that are a hit in the common mechanism) can only be synthesized if the provider determines that it will be used for legitimate purposes. In the absence of an affirmative determination by the provider of the benchtop DNA synthesis machine, the machine should be unable to synthesize pathogen or toxin DNA.

Because widely available benchtop DNA synthesis machines are still to come, it is difficult to anticipate how they will be used and the business models that will support their use. This uncertainty provides an opportunity to explore the possibility of a norm against creation of some pathogen and toxin DNA on benchtop machines.

The Consortium should also consider models for building security directly into benchtop devices. For example, a more decentralized system might be pursued whereby the common screening mechanism is integrated into each benchtop DNA synthesis machine (though this wider distribution may further complicate security). Alternatively, a centralized version of the common mechanism, such as a mechanism housed by the Consortium or an affiliated international organization, could be made available to receive DNA sequence queries and return results. In either of these cases, the provider of the benchtop DNA synthesis machines would not be actively involved in synthetic DNA screening. Therefore, these machines should be unable to synthesize pathogen or toxin DNA on their own; a hit in the common mechanism would indicate that synthesis should not proceed.

Another possibility in the future is that certified, legitimate users of pathogen and toxin DNA, such as academic researchers studying virology in a secured laboratory, could request an “unlocked” benchtop DNA synthesis machine that would be allowed to synthesize DNA without DNA sequence screening. Such a scenario, however, would require additional security measures to limit the machine’s use to legitimate users, and only for their legitimate research.

Oversight, policies and partnerships for establishing synthetic DNA screening as a global norm

Recommendation 1

The Consortium should be funded as an independent technical entity for at least two years so that it can immediately start work to meet the goal of developing the common DNA sequence screening mechanism and providing it to DNA providers and providers of benchtop DNA synthesis machines by 2021.

The technical work of establishing expert consensus on the set of sequences of pathogen and toxin DNA and developing screening algorithms should begin immediately. These expert activities will continue (see Box 2) as oversight, organizational structure, partnerships and the global norm for synthetic DNA screening become established.

Recommendation 2

In early-to-mid 2020, NTI and the World Economic Forum should convene senior leaders from governments, companies and international organizations to explore options for the sustainable oversight of the Consortium and maintenance of the proposed DNA sequence screening mechanism. These options may include developing synthetic DNA screening as a new mandate for an existing international entity or the creation of a new organization to take on this mandate.

The common DNA sequence screening mechanism will require oversight from an internationally recognized body to 1) promote its adoption, implementation and legitimacy; 2) ensure that appropriate security measures are taken; and 3) assure ongoing operation of the Consortium and availability of the common mechanism into the future.

Recommendation 3

In partnership with the new or existing organization focusing on this work, the technical Consortium should work with states, international organizations, industry groups, universities and others to pursue opportunities to strengthen synthetic DNA screening as a global norm and standard among governments, researchers, institutions and providers of DNA and benchtop DNA synthesis machines.

Concurrent with the development of a common mechanism, national governments, international organizations and industry groups can strengthen the global norm for synthetic DNA screening practices. The Consortium and associated organizations or oversight bodies can work with these groups to support the endorsement, adoption, and integration of the common mechanism for synthetic DNA sequence screening into existing frameworks.

National governments should support the use of a common DNA sequence screening mechanism. For example, governments could:

- Require, through legislation or regulations, synthetic DNA screening practices and certification of DNA providers and providers of benchtop DNA synthesis machines within their borders. DNA providers and providers of benchtop DNA synthesis machines that provide pathogen or toxin DNA may need additional guidance on how to evaluate hits from the common mechanism and how to determine which users are authorized to receive pathogen or toxin DNA, which may differ by country.

- Limit legal and financial liability for organizations that adhere to the common DNA sequence screening mechanism.

- Raise awareness among law enforcement personnel, export control officials and other relevant authorities about risks related to potential misuse of synthetic DNA and identify an agency-level national point of contact for providers if and when they recognize that someone is intentionally attempting to misuse pathogen or toxin DNA. National activities could be coordinated with existing international groups, such as INTERPOL, the Biological Weapons Convention (BWC), United Nations Security Council Resolution 1540, World Health Organization (WHO) Joint External Evaluations, the Australia Group, and the Global Partnership Against the Spread of Weapons and Materials of Mass Destruction.

- Provide direct financial support to companies for adopting synthetic DNA screening practices.

Similarly, other vital actors, such as *research funders, technology investors, industry groups, insurers and other relevant institutions* should also actively bolster the global norm for synthetic DNA screening practices and effectively incentivize compliance. For example:

- DNA providers could certify that they use the common DNA sequence screening mechanism to screen orders for the presence of pathogen or toxin DNA and only provide pathogen or toxin DNA to legitimate users.

- Companies, institutions and researchers who manufacture, sell, purchase or otherwise use benchtop

DNA synthesis machines could certify that they have a process in place to prevent those machines from being used to illegitimately synthesize pathogen or toxin DNA.

– Research funders could require synthetic DNA screening practices as a mandatory element of funding and grant-making, such that grantees would be required to purchase synthetic DNA and benchtop DNA synthesis machines from providers that adhere to the common mechanism for DNA sequence screening.

– Institutions could integrate requirements for synthetic DNA screening practices into biosafety and biosecurity practices and provide training on the potential risks of accidental and deliberate misuse of synthetic DNA and on synthetic DNA screening best practices.

– Insurers and issuers of bonds could incorporate use of the common DNA synthesis screening mechanism into insurance policies and bond ratings.

– Non-governmental actors and professional organizations could require synthetic DNA screening practices for issuing ratings, accreditations, awards and seals of approval that impact institutions and businesses.

Finally, *international organizations* should actively promote the norm for synthetic DNA screening by driving recognition and adoption of the common DNA sequence screening mechanism. For example:

– Leadership from relevant international organizations, such as the United Nations, WHO, World Organisation for Animal Health (OIE), International Organization for Standardization, World Intellectual Property Organization and Organisation for Economic Co-operation and Development, joining efforts with the World Economic Forum, should raise awareness, disseminate guidance and incentivize use of the common DNA sequence screening mechanism.

– WHO and the OIE could integrate requirements for synthetic DNA screening practices by DNA providers and providers of benchtop DNA synthesis machines into public health and animal health-related guidance, such as the International Health Regulations, as well as guidance and training related to laboratory biosecurity and biosafety.

– The Australia Group could ensure that the common DNA sequence screening mechanism captures its export requirements for pathogen and toxin DNA, and that use of the common mechanism facilitates compliance.

– Other international organizations could also support consistency between the common DNA sequence screening mechanism and their guidance and practices, integrating synthetic DNA screening practices and related training into their frameworks. These groups might include the United Nations Office for Disarmament Affairs, the BWC Implementation Support Unit, the Global Partnership Against the Spread of Weapons and Materials of Mass Destruction, the Global Health Security Agenda, United Nations Security Council Resolution 1540, and other relevant international bodies, treaties and international organizations.

Development of the common DNA sequence screening mechanism will expand beyond the current system for synthetic DNA screening practices. Partners, sponsors and supporters at every level will help ensure that screening practices become an established global norm. DNA screening will be an important safeguard against the accidental or deliberate misuse of pathogen and toxin DNA as access to synthetic DNA rapidly expands and benchtop machines become a reality.

“DNA screening will be an important safeguard against the accidental or deliberate misuse of pathogen and toxin DNA as access to synthetic DNA rapidly expands.”

Conclusion

A global approach is urgently needed to safeguard against the potential for accidental or deliberate misuse of DNA synthesis technologies. In recent years, the rapidly declining price of synthetic DNA has expanded its accessibility, providing opportunities for technological and economic advances but also increasing the potential for misuse. While some DNA providers have voluntarily implemented sequence screening procedures to help limit access to pathogen or toxin DNA to legitimate users, economic disincentives to these practices are growing. At the same time, benchtop DNA synthesis machines could further expand the availability of synthetic DNA around the world and procedures to screen DNA orders or build in mechanisms to prevent specific sequences have not yet been developed for this segment of the industry. This report and its recommendations describe a framework to establish sequence screening as a global norm.

The recommendations call for two activities to be pursued in parallel. The technical, multistakeholder Consortium, tasked with developing the common mechanism for DNA sequence screening, should begin its work as soon as possible. At the same time, a new global entity should be formed to oversee the Consortium and help establish DNA sequence screening as a global norm, either as a new mandate for an existing international entity or through the creation of a new organization to take on this mandate. NTI and the World Economic Forum will convene senior leaders from governments, companies and international organizations to explore options for such an organization. Once established, this international entity, bolstered by the technical Consortium, should work with national governments, international organizations, industry groups, funders and others to support the endorsement and adoption of the common mechanism for DNA sequence screening.

> **“The international entity described will serve as a focal point for expertise, discussion and action to address biological risks associated with advances in technology, now and into the future.”**

In the coming years, DNA synthesis technologies and related tools will continue to change rapidly, and access to these capabilities will expand further. These and other current and future life sciences technologies will not only help drive breakthroughs and economic growth throughout the world, but also hold the potential for misuse. Understanding this changing landscape in real time and working internationally to address identified risks will be critical. The international entity described here will serve as a focal point for expertise, discussion and action to address biological risks associated with advances in technology, now and into the future. The recommendations in this report are an important first step to enabling safer and more secure life sciences development for the good of humanity.

Appendices

A. Working Group members

Members of the Working Group on Preventing Illicit Gene Synthesis participated in their personal capacities. The opinions expressed in this report and the actions supported by the World Economic Forum and NTI do not necessarily reflect the views of the members' respective employers, other affiliations or governments.

Evan Appleton
Postdoctoral Research Fellow,
Harvard Medical School, USA

Patrick Boyle
Head, Codebase, Ginkgo Bioworks, USA

Tim Brears
Chief Executive Officer, Evonetix, United Kingdom

Yizhi Cai
Chair in Synthetic Genomics, University of Manchester, United Kingdom

Marc Casper
President and Chief Executive Officer, Thermo Fischer Scientific, USA

George Church
Director, Lipper Center for Computational Genetics, Harvard Medical School, USA

Drew Endy
Associate Professor, Department of Bioengineering, Stanford University, USA

James Diggans
Director, Bioinformatics and Biosecurity,
Twist Bioscience, USA

Jay Flatley
Chairman, Illumina, USA

Douglas Friedman
Executive Director, Engineering Biology Research Consortium, USA

John Glass
Professor and Leader, Synthetic Biology and Bioenergy Group, J. Craig Venter Institute, USA

Marcus Graf
Director of Operations, Synthetic Biology, Thermo Fisher Scientific, Germany; Chair, International Gene Synthesis Consortium

Avril Haines
Senior Research Scholar, Columbia University, USA

Margaret A. Hamburg
Foreign Secretary, National Academy of Medicine, USA

Christian Happi
Professor of Molecular Biology and Genomics, Redeemer's University, Nigeria

Wilmot James
Visiting Professor of Political Science and (Non-Clinical) Pediatrics, Columbia University, USA

Tom Knight
Co-Founder, Ginkgo Bioworks, USA

Lee Sang-Yup
Distinguished Professor and Dean, Korea Advanced Institute of Science and Technology (KAIST), Republic of Korea

Emily Leproust
Co-founder and Chief Executive Officer,
Twist Bioscience, USA

Amy Liao
President, GENEWIZ, USA

Jason Matheny
Founding Director, Center for Security and Emerging Technology (CSET), Georgetown University, USA

Piers Millett
Vice-President, Safety and Security, iGEM Foundation, USA

Sergey Netesov
Head, Bionanotechnology Laboratory, Novosibirsk State University, Russian Federation

Peer Schatz
Senior Adviser, QIAGEN, Germany

Pamela Silver
Professor of Biochemistry and Systems Biology, Harvard Medical School, USA

Rakesh Sood
Distinguished Fellow, Observer Research Foundation, India

Xu Xun
President, Research, BGI, People's Republic of China

B. Mechanism definitions

The mechanism seeks to prevent DNA synthesis of pathogen or toxin DNA that is not for legitimate use. The definitions here provide a starting point for the mechanism and are based on practices honed by the IGSC and other DNA providers that currently screen DNA sequences. As described above, the initial set of sequences developed for this mechanism will be generated based on international expert consensus and may be a small set of sequences unambiguously linked to pathogenicity or toxicity. The Consortium and other associated actors will likely need to revisit and revise these definitions as information is gained, DNA synthesis technologies are developed, screening methods are improved and the mechanism is updated.

– DNA synthesis subject to DNA sequence screening includes both single-stranded and double-stranded DNA. The Consortium should work to determine a lower limit on the length of DNA that should be screened. As screening methods improve, screening may also be expanded to include synthesis of shorter single-stranded DNA ("oligos") that are synthesized in arrays or pools designed for assembly into longer stretches of double-stranded DNA.

– Pathogen or toxin DNA

    - Would include DNA sequences that are unambiguously unique to pathogens already included on authoritative lists (i.e. have high homology to sequences from listed pathogens and higher homology to such sequences than to sequences from non-pathogen organisms) or encode a listed toxin.

    - May not include all DNA sequences that match sequences of listed pathogens – for example, bacterial genes that do not endow or enhance pathogenicity.

    - Initially, would not include DNA sequences encoding enzymatic pathways and other cellular processes that may allow production of unregulated toxic or illegal compounds, unless those sequences are found in listed pathogens or encode listed toxins.

    - Initially, would not include DNA sequences predicted to or likely to encode pathogenicity factors or other harmful functions, unless those sequences are found in listed pathogens.

– DNA provider is an entity (often a commercial company) that sells or otherwise provides custom-synthesized DNA. It includes entities that sell or provide DNA synthesized by a third party and companies that assemble double-stranded DNA from oligos purchased from a third party.

– Benchtop DNA synthesis machine is capable of high-quality DNA synthesis and is intended to be installed at the end-user's facility. It is directly available to the end user for custom DNA synthesis and does not include liquid-handling machines that do not synthesize oligonucleotides.

– Provider of benchtop DNA synthesis machines is an entity that sells or resells benchtop DNA synthesis machines.

– Legitimate users include those working in laboratories permitted by appropriate authorities to work with listed pathogens or toxins or with pathogen or toxin DNA and that have biosafety and containment practices consistent with international norms. Such authorization will vary based on country and context.

C. Future challenges and opportunities for the common DNA sequence screening mechanism

The common mechanism, as described above, is initially designed to capture DNA sequences that match listed pathogens or toxins, namely those pathogens or toxins listed by different authorities as particularly dangerous and unambiguously linked to pathogenicity or toxicity. Although the mechanism is also envisioned as a single consensus mechanism designed for broad use, it is designed to undergo regular scrutiny and revision by the Consortium, which can choose to expand or reduce the contents of the set of sequences of concern and can determine how screening is conducted and what type of DNA products should be screened. Several areas have been identified that the Consortium should consider over time to determine if a workable international expert consensus can be achieved:

– DNA sequences that are not associated with currently known pathogens and toxins may be identified in publicly available literature as harmful or predicted to cause harm. These include sequences that may endow or enhance pathogenicity or toxicity in pathogens or non-pathogen organisms or metabolic pathways for production of toxic compounds. More broadly, DNA sequences that encode a wide range of functionality, such as gene drives (genetic elements that can spread in naturally occurring populations of organisms) or degradation pathways for critical infrastructure materials, could be considered harmful. Other novel risks are likely to be described in the future. Such publicly available DNA sequences could be added to the common mechanism in the future if there is some international consensus to do so.

– DNA sequences ultimately confer some risk because the proteins they encode provide some functionality to the organism. It is currently difficult, however, to estimate how much the protein (and the underlying DNA sequence) may be changed or substituted while preserving functionality. As advances are made in understanding links between DNA sequence and functionality, DNA sequence screening methods may need to be updated.

– It is currently difficult to screen short individual oligos, but it is increasingly common for arrays or pools of oligos to be ordered for assembly into gene- and genome-length double-stranded DNA. As sequence screening methods improve, these orders could be screened using the common mechanism. If and when it becomes feasible for other types of oligo orders to be screened, the mechanism can be further updated.

– A key feature of synthetic biology is that DNA sequences are designed using digital tools and organisms are often optimized using a “design-build-test-learn” cycle. Although the common mechanism would initially be offered exclusively to synthetic DNA providers and providers of benchtop DNA synthesis machines, it could also be made available to other synthetic biology companies and entities such as providers of bioinformatic resources and DNA design services or “biofoundries,” institutions that facilitate the design-build-test-learn cycle for organism engineering. Such a system would extend DNA sequence screening practices to multiple levels to better ensure that pathogen and toxin DNA is not accidentally or deliberately misused, even if an actor can circumvent hurdles related to DNA synthesis. Such an expansion should be carefully considered to determine if it would exacerbate security concerns.

– As funding allows and as partnerships are formed in the future, the Consortium could consider developing more customized tools for synthetic DNA screening in different contexts, such as screening mechanisms that include decision-making support for the export of synthetic DNA, are designed for specific country or regional contexts or are customized for specific purposes (for example, a system that captures a broader set of risks for use in more restrictive contexts). Such approaches could incorporate appropriate customer evaluation, certification or licensure measures, if and when they are developed. Future methods could include more distributed approaches to certify the legitimacy of synthesis orders.

Contributors

Elizabeth E. Cameron
Vice-President, Global Biological Policy and Programs,
Nuclear Threat Initiative, USA

Sarah R. Carter
Principal, Science Policy Consulting LLC, USA

Jacob L. Jordan
Senior Director, Global Biological Policy and Programs,
Nuclear Threat Initiative, USA

World Economic Forum

Ryan Morhard
Lead, Global Health Security, International Organizations
and IGWELs

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World Economic Forum
91–93 route de la Capite
CH-1223 Cologny/Geneva
Switzerland

Tel.: +41 (0) 22 869 1212
Fax: +41 (0) 22 786 2744

contact@weforum.org
www.weforum.org