NTI:bio

Benchtop DNA Synthesis Devices:

Capabilities, Biosecurity Implications, and Governance

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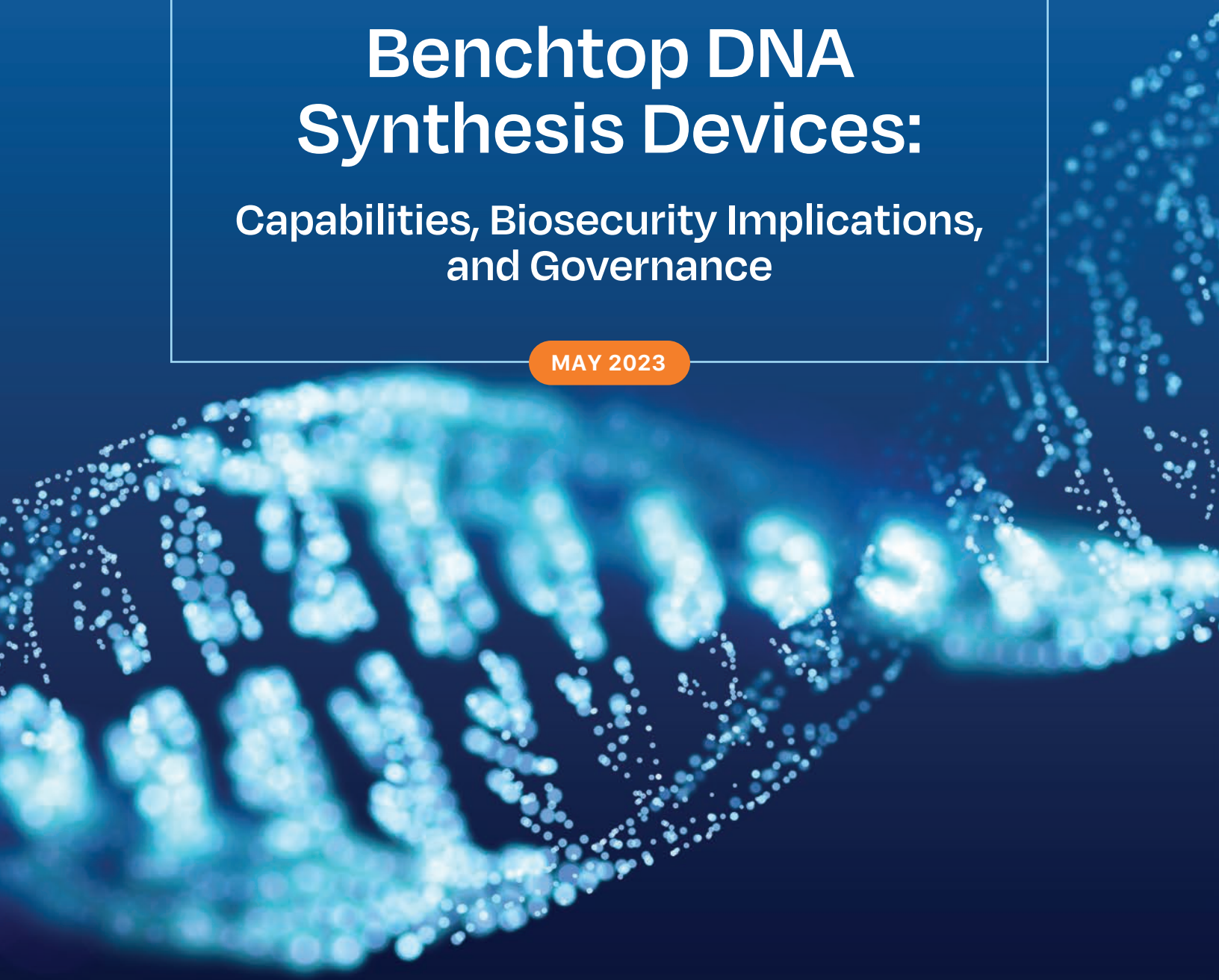

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Open Philanthropy

About the Nuclear Threat Initiative
The Nuclear Threat Initiative is a nonprofit, nonpartisan global security organization focused on reducing nuclear and biological threats imperiling humanity.

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Executive Summary

Synthetic DNA is used by bioscience laboratories around the world and plays a fundamental role in a wide range of science and biotechnology advances. DNA synthesis technology—which makes it possible to "print" DNA with any user-defined sequence—enables researchers to study and engineer biological systems to better understand how they work. It is also essential for a wide range of biotechnology advances, from agricultural products and pharmaceuticals to advanced fuels and other biomanufacturing applications. For example, this capacity has been critical for rapid characterization of new and emerging pathogens during the COVID-19 pandemic, as well as speedy development of diagnostics, vaccines, and other medical countermeasures. Access to synthetic DNA is crucial to these advances and to the broader bioeconomy.

However, increased access to synthetic DNA resulting from new, more widely available technologies to produce it—combined with scientific advances in our understanding of pathogens—may also empower malicious actors by providing the building blocks of potentially dangerous biological agents. As DNA synthesis technologies advance, governments, industry, and other stakeholders must act urgently to develop the safeguards necessary to prevent accidental or malicious misuse.

Currently, nearly all synthetic DNA is produced by centralized providers that screen their customers and orders to help ensure that DNA with a potentially harmful sequence is not sold to customers without a legitimate use for it. However, a new generation of benchtop DNA synthesis devices—machines designed to be used on any lab workbench and without special equipment—will soon enable users to more easily print DNA in their own laboratories. This emerging technology has the potential to disrupt the centralized synthesis market and its associated biosecurity practices by driving DNA acquisition toward a more decentralized model. Without appropriate oversight, these devices could be used by bad actors to obtain pathogen or toxin DNA and to facilitate pathogen engineering.

Drawing on more than 30 interviews with experts from benchtop DNA synthesis companies, the broader biotechnology industry, the biosecurity and bioscience research communities, and other sectors, this report addresses key questions critical to the understanding of the current status of benchtop DNA synthesis device capabilities and the broader implications for biosafety and biosecurity.

Traditional DNA Synthesis Versus Benchtop Devices

For decades, researchers have been able to order high-quality, low-cost synthetic DNA from companies that produce custom DNA to match customer needs. Customers submit orders through an online portal specifying the required DNA strand sequence and length, and companies synthesize the DNA, which is then shipped to the customer. This centralized process provides an opportunity for oversight: although customers can order DNA with any sequence, most DNA providers screen the ordered sequence to determine whether it matches pathogen or toxin DNA.

New benchtop DNA synthesis devices will enable users to obtain synthetic DNA more rapidly by synthesizing it in their own laboratories. This on-demand, decentralized production of synthetic DNA also allows more privacy, which could enable a user to create pathogen or toxin DNA without detection. These new benchtop devices will require new thinking about governance and oversight to guard against exploitation by malicious actors and catastrophic accidents.

Key Findings

These findings represent a snapshot in time for DNA synthesis capabilities and the associated risk landscape, which will evolve as the science and technology advance.

What is the current status of benchtop DNA synthesis device capabilities, and how will these capabilities evolve over the next 5–10 years?

- Current benchtop synthesis devices can reliably print DNA up to 200 bases in length, but it is very likely that newer devices will be able to reliably and automatically produce double-stranded DNA (dsDNA) up to approximately 5,000–7,000 base pairs in length within the next 2–5 years. Over the next 5–10 years, benchtop device advances may enable reliable synthesis of dsDNA up to 10,000 base pairs long. As a reference point, there are a few viral genomes that are shorter than 7,000 base pairs, but the vast majority are between 10,000 and 200,000 base pairs in length. Bacterial genomes are longer than 1 million base pairs.
- Technology developments that enable benchtop synthesis capabilities include advances in laboratory automation as well as new enzymatic DNA synthesis approaches, which are easier to use and require less hazardous reagents.
- Key factors limiting the capabilities of benchtop devices include sequence fidelity of the DNA—i.e., how well the synthesized version matches the intended sequence—and fundamental limits on capabilities to assemble DNA sequences into long fragments by using automated systems.
- Although the extent of the market for benchtop devices remains unclear, likely customer benefits include speed of DNA synthesis and potential confidentiality of requested sequences.

What are the biosecurity implications of these developments?

- Easy access to dsDNA of 5,000–7,000 base pairs in length is likely to increase the potential for misuse of synthetic DNA because it will lower one of the technical hurdles to synthesizing or engineering pathogens.
- Notwithstanding the risks associated with benchtop devices, a nefarious actor seeking to generate or otherwise engineer pathogens to cause harm would face significant technical hurdles beyond access to dsDNA, including

the challenges associated with assembling a full pathogen genome—generating DNA that encodes a pathogen's full genetic blueprint; "booting up" a functional pathogen; or altering or enhancing the properties of a pathogen beyond those found in nature.

What tools and oversight mechanisms can most effectively mitigate biosecurity risks?

- Oversight of benchtop DNA synthesis devices can meaningfully reduce biosecurity risks without unduly limiting the benefits to legitimate bioscience and biotechnology research and development.
- Many potential oversight mechanisms depend on device manufacturers to screen customers to ensure user legitimacy and to screen the DNA sequences that are requested, which is consistent with current screening practices by traditional DNA providers. There will likely be tension between the preferences of some benchtop device users to keep locally printed DNA sequences confidential and the need for biosecurity safeguards to reduce the risk that these devices will be misused.
- A range of incentives, including government guidelines, regulations, and financial support, should be considered to encourage adoption of biosecurity best practices by device manufacturers and users.

Recommendations

Drawing on insights garnered from expert interviews conducted for this study, the report authors developed the following recommendations. These recommendations do not necessarily reflect the individual views of the experts consulted for this report.

There are currently no formal guidelines for oversight of benchtop DNA synthesis technology, and no codified approach internationally. The only safeguards in place for benchtop devices are voluntarily implemented by some manufacturers.

Benchtop synthesis device manufacturers should conduct rigorous customer screening for those who want to purchase or use their devices.

- Manufacturers should screen customers prior to selling the device to ensure that each customer is a legitimate user.
- Customer screening should extend beyond initial purchase and include ongoing verification of end users.

Benchtop synthesis device manufacturers should ensure that each DNA fragment produced by the device undergoes rigorous sequence screening.

- Where feasible, manufacturers should use a direct oversight approach in which the benchtop device automatically reports sequences for screening to the manufacturer prior to synthesis.
- Device manufacturers should follow DNA sequence screening standards that at least match a minimum standard used by traditional DNA providers.

Governments should provide clear guidelines, strong incentives, and, in some cases, regulations for benchtop device manufacturers to incorporate vigorous customer and sequence screening.

- In the near term, governments in countries around the world should develop voluntary guidance to set clear expectations regarding customer and sequence screening practices by benchtop DNA synthesis device manufacturers which are consistent with guidelines related to traditional DNA providers.
- Within 2 years, national governments should plan to implement regulatory requirements for selling or operating benchtop DNA synthesis

devices within their borders. Requirements should cover devices that are capable of automatically synthesizing and assembling DNA to generate dsDNA with high sequence fidelity at a length of 200 or more base pairs.

- To support both voluntary and mandatory DNA synthesis screening practices, governments should provide guidance, resources, and/or tools to reduce ambiguity about which DNA sequences constitute a risk subject to additional scrutiny and oversight.
- Governments should provide financial incentives to support adherence to DNA synthesis screening guidance and compliance with regulations.

Civil society, private funders, journals, and the scientific community should provide tools and incentives for robust biosecurity practices and responsible oversight by benchtop device manufacturers. An international organization should support governance efforts by civil society and governments to ensure a coherent oversight approach.

- Civil society and the scientific research community should develop resources and tools to ensure that customer and sequence screening are as easy as possible for device manufacturers and that best practices are constantly improving.
- Civil society, the scientific research community, and industry should convene discussions about the trade-offs between the desire for privacy by some benchtop synthesis device users and the risks posed by inadequate biosecurity safeguards for this technology.
- Private funders, such as philanthropic organizations and venture capital firms, should require that funded researchers purchase benchtop DNA synthesis devices only from manufacturers that conduct rigorous customer and sequence screening. Journals could put in place similar requirements for publication of research.
- Civil society, private funders, and insurers should work together to explore liability and insurance mechanisms to encourage adoption of biosecurity best practices by benchtop device manufacturers and device users.
- An international organization, such as the International Biosecurity and Biosafety Initiative for Science (IBBIS), should track and support civil society and government efforts to ensure a coherent oversight approach.

DNA synthesis technology is fundamental to bioscience and biotechnology advances. The field is rapidly changing, with active development, commercialization, and market expansion of benchtop DNA synthesis devices. The new generation of these devices promises faster and more convenient access to DNA for researchers and biotechnology developers, facilitating valuable discoveries and innovation. However, expanded access also will reduce barriers for bad actors, including those seeking to cause catastrophic harm.

Policymakers and others must act quickly, on an international basis, to ensure that benchtop synthesis devices and the companies that provide them operate with appropriate biosecurity rules, expectations, and practices. The actions recommended in this report can help safeguard DNA synthesis technology against accidental misuse and deliberate abuse. By establishing these norms early, benchtop DNA synthesis devices can be used in a way that realizes their full benefits while minimizing biosecurity risks.

Introduction

Providers of synthetic DNA offer a key service that underpins basic and applied research in bioscience laboratories around the world. DNA synthesis technology—which enables the production of made-to-order DNA based on any user-defined sequence—plays a fundamental role in molecular biology laboratories, enabling researchers to study and engineer biological systems to better understand how they work. It is also essential for a wide range of biotechnology advances, from agricultural products and pharmaceuticals to advanced fuels and other biomanufacturing applications. For example, DNA synthesis technology has been critical for rapid characterization of new and emerging pathogens during the COVID-19 pandemic, as well as speedy development of diagnostics, vaccines, and other medical countermeasures. Access to synthetic DNA is crucial to these advances and to the broader bioeconomy.

Over the past 20 years, synthetic DNA has driven many biotechnology advances as it has become increasingly available at higher quality and exponentially declining costs, primarily from companies and other DNA suppliers that provide single-stranded DNA (oligos) or dsDNA, which are custom produced with sequences specified by each user.

In addition to the myriad benefits that synthetic DNA offers, this tool for basic and applied research, combined with scientific advances in our understanding of pathogens, may also empower malicious actors to cause harm. In particular, some security experts are concerned that nefarious actors with the appropriate training could exploit DNA synthesis services to create pathogens or toxins from scratch *(de novo)* or engineer pathogens with new, more dangerous traits. While this is still quite technically challenging, some experts are concerned that the technical hurdles to de novo pathogen synthesis and pathogen engineering will continue to drop over the next 10–20 years and that this will pose a growing risk over time.

To safeguard DNA synthesis technology—and to help ensure that the building blocks of dangerous pathogens do not fall into the wrong hands—many DNA providers voluntarily screen their customers and their orders to help ensure that DNA sequences corresponding to key elements of pathogens or toxins are not sold to customers without a legitimate use for them. The U.S. government issued guidance in 2010 to encourage DNA synthesis providers to conduct such screening[1] and published a proposed revised version of this guidance for public comment in 2022.[2] The revised Screening Framework Guidance provides updates and advances the discussion on new DNA synthesis technologies and approaches, but it has not yet been finalized and it is unclear how this new guidance will affect screening practices.

The emergence of a new generation of benchtop DNA synthesis devices, which will enable users to more easily "print" DNA in their own laboratories, constitutes an important development for DNA synthesis. This rapidly evolving technology has the potential to upend the centralized DNA synthesis market and its associated biosecurity practices by driving DNA acquisition toward a more decentralized model. While decentralized DNA synthesis capabilities could offer significant benefits, if existing oversight provisions and biosecurity safeguards—such as customer and order screening—are not incorporated into these new tools, this emerging technology could significantly increase the risks of deliberate abuse or accidental misuse of synthetic DNA.

BioXp® Molecular Biology Workstation
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Experts in the bioscience, biotechnology, and security communities have paid increasing attention to next-generation benchtop synthesis devices as this technology has matured and as new devices have become available on the commercial market. Many of these experts are concerned about the potential biological risks these devices could pose if they are not properly safeguarded with rigorous biosecurity measures. However, to date there has been no public assessment of the current state of this technology and how it is anticipated to evolve over the next 5–10 years. Nor

has there been an assessment of the impact of these developments on biosafety and biosecurity risks. The authors of this report set out to answer these questions in conducting their research.

This report provides an in-depth analysis of benchtop DNA synthesis devices, with a focus on three key topics. The first section outlines the current status of benchtop DNA synthesis technology and how it is likely to evolve. It also discusses the market for these devices, including key drivers of commercial demand. The next section discusses the biosecurity implications of current and near-future benchtop DNA synthesis devices. The goal is to clarify and discuss in concrete terms the ways that benchtop devices could make it easier for a broad range of actors to engineer pathogens and the hurdles that those actors would still need to overcome. The third section offers a range of perspectives on governance tools and oversight approaches that could be effective for mitigating biosecurity risks associated with benchtop DNA synthesis capabilities. These first three sections are based on interviews with more than 30 experts in the field, and the final section of this report presents recommendations from the authors on effective approaches for safeguarding benchtop DNA synthesis technology and preventing its exploitation by malicious actors. The recommendations presented in this report were developed by the authors alone and do not necessarily represent the views of the experts interviewed.

History and Context

In 2018, the Biological Innovation and Risk Reduction Initiative—a project developed by Nuclear Threat Initiative (NTI) to address emerging biological risks associated with rapid technology advances[3]—identified misuse of synthetic DNA as a critical biosecurity risk and initiated a project with the World Economic Forum (WEF) to develop an international approach to mitigate it.[4] NTI and WEF have since established the Technical Consortium for DNA Synthesis Screening,[5] an international group of technical and policy experts from the DNA synthesis industry, the broader synthetic biology and biosecurity communities, and other key stakeholders. NTI, WEF, and the Technical Consortium have worked to develop best practices and tools to support more effective customer and sequence screening by DNA providers, including an international Common Mechanism for DNA synthesis screening. In 2023, NTI will further these efforts by launching the International Biosecurity and Biosafety Initiative for Science (IBBIS) as an independent entity with an initial focus on DNA synthesis screening.[6] This report builds on these efforts by offering an in-depth analysis of benchtop synthesis developments, which can in turn inform the broader efforts to strengthen DNA synthesis screening practices and governance.

Methodology

This report draws on more than 30 structured interviews with experts from benchtop DNA synthesis companies, synthetic biology, the biosecurity community, bioscience research, and other sectors. The authors also convened a virtual workshop in December 2021, which involved study participants and additional experts to discuss preliminary findings and recommendations based on the interview process. (A list of interviewees and other participants is included in Appendix A.) The first three sections of this report draw heavily on the expert opinions and perspectives that were gathered during the project. The report incorporates and reflects the range of views shared by the experts consulted by the authors, but there was no attempt to generate consensus among that group.

Benchtop DNA Synthesis: Current and Anticipated Capabilities

Recent technical advances in DNA synthesis promise to bring about a new generation of benchtop DNA synthesis devices that may change how researchers obtain synthetic DNA. To better understand this rapidly evolving technology, this project was guided by several basic underlying questions:

- **What is the status of benchtop DNA synthesis device capabilities, and how will it evolve over the next 5–10 years?** What are the underlying enabling technologies, and what are their limitations?
- **What is the market for benchtop devices?** How widespread are they likely to become, and how will they be used?

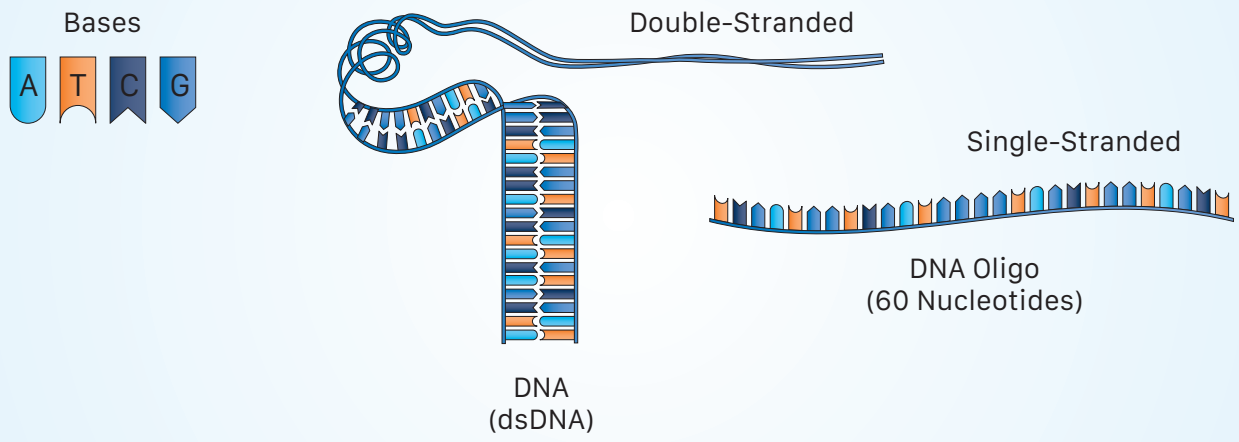
Access to synthetic DNA is critical for life science research in laboratories around the world. Scientists typically order DNA online and specify the exact sequence of nucleotides (A's, T's, G's, and C's) that they need. Ordered DNA can range in length from 10–20 nucleotides to thousands of nucleotides or more. To meet these needs, nearly all DNA synthesis is conducted in high-throughput commercial facilities that produce and ship DNA with sequences specified by the customer. This centralized production, led by DNA providers such as IDT, Twist Biosciences, and Thermo Fisher, has enabled access to reasonably priced, reliable DNA for life science applications over the past 20 years.[7] However, recent advances in benchtop DNA synthesis capabilities may expand access to synthetic DNA by enabling a wider range of scientists to synthesize DNA—that is, to print their desired sequence—within their laboratories instead of relying on centralized DNA providers.

Current and Near-Future Capabilities of Benchtop DNA Synthesis Devices

Although benchtop DNA synthesis devices have been available for decades, recent technology advances are enabling development and commercialization of a new generation of benchtop devices that are likely to be qualitatively different from their predecessors. These next-generation devices are much easier to use, will soon have the capability to automatically generate longer stretches of DNA, and will require considerably less laboratory infrastructure.

Over the next 2–5 years, it is very likely that the most capable benchtop DNA synthesis devices will be able to reliably produce dsDNA up to approximately 7,000 base pairs long, and within the next 5–10 years, they may be able to produce dsDNA of up to 10,000 base pairs. The length of DNA that a benchtop device can produce is important because it determines the range of potential applications (see Figure 1: What Is DNA?). Single-stranded DNA—often referred to as

Figure 1: What Is DNA?



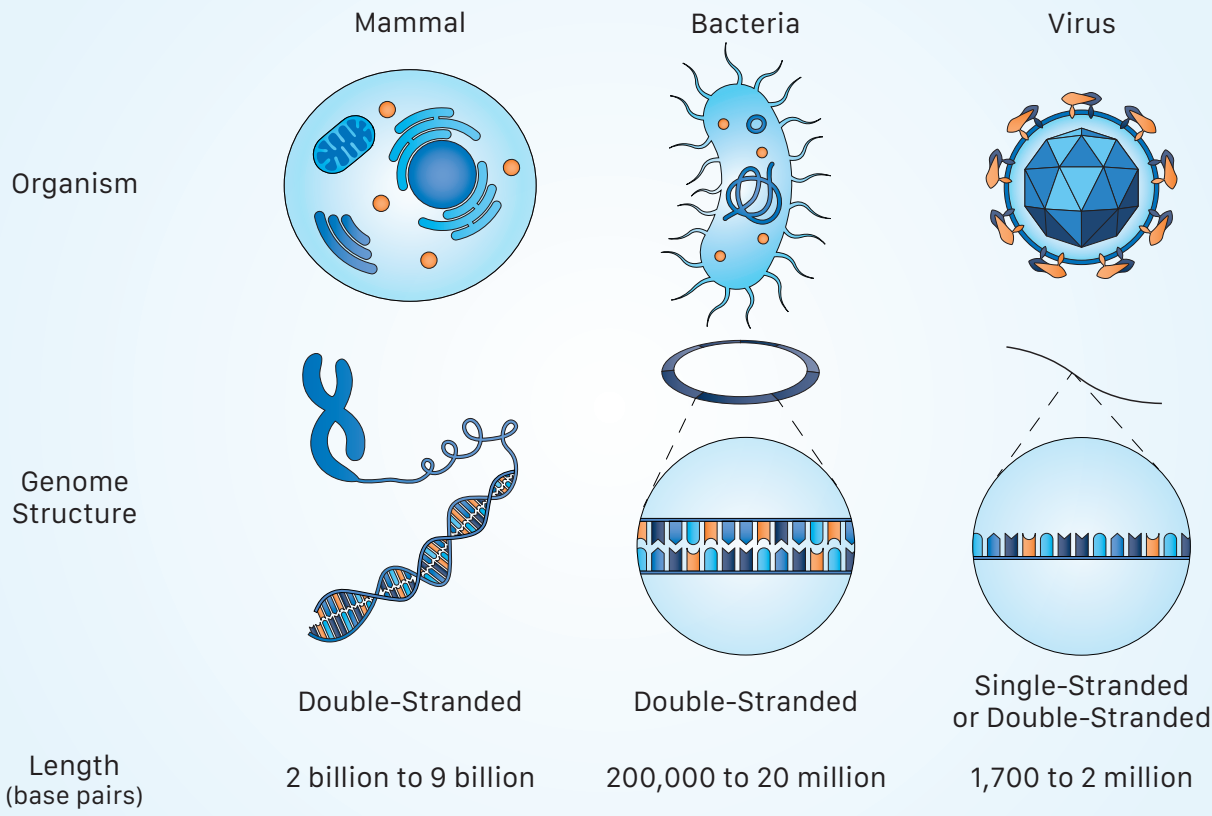
DNA is the blueprint for life on earth. Strands of DNA (deoxyribonucleic acid) are composed of individual nucleic acid "bases" (often abbreviated as A, G, T, or C), which when interpreted in sequence comprise the "genetic code." Single strands of DNA will pair and form "double-stranded DNA" (dsDNA) when two strands have complementary bases. Short stretches of single-stranded DNA are referred to as "oligos."

"oligos" and often less than ~60 nucleotides—is nearly ubiquitous in molecular biology labs and is used for a wide range of applications, such as DNA sequencing and polymerase chain reaction (PCR) (which makes many copies of a DNA fragment). Current benchtop DNA synthesis devices, using technology that has been available since the 1990s, can synthesize oligos to meet these needs.

Longer dsDNA—often 500–5,000 base pairs—typically encodes a gene fragment, an entire gene, or sometimes several genes and is used in a wide range of gene expression studies and synthetic biology applications. Next-generation benchtop synthesis devices will be able to produce this longer dsDNA for such applications.

Very long stretches of synthetic dsDNA—more than ~7,000–10,000 base pairs—are less commonly used, and generating them is more complex and challenging. It is these longer stretches of dsDNA that are most likely to raise biosecurity concerns because they could encode the entire genome of a virus (see Figure 2: What Is a Genome?). There are some viral genomes that are shorter than 7,000 base pairs, but most are longer—on the order of 10,000–200,000 base pairs. It is possible to assemble shorter DNA fragments into these longer

Figure 2: What Is a Genome?



A genome is the essential genetic information that defines how an organism functions. Mammalian genomes (including human ones) and bacterial genomes are composed of double-stranded DNA, but viral genomes are more diverse. Viruses can have genomes that are made of DNA or RNA (similar to DNA but with different nucleic acid bases) and can be single-stranded or double-stranded. The length of the genome, measured in the number of bases (nucleoties) or base pairs, is highly variable, but is usually smaller in viruses than in other types of organisms.

lengths, but the process requires skill and expertise and is not amenable to automation. For the foreseeable future—at least the next 10 years—it is unlikely that benchtop DNA synthesis devices will be able to automatically generate dsDNA at these greater lengths.

Enabling Technologies for Benchtop Synthesis Device Advances

The state of the art for making longer stretches of DNA includes synthesis of short, single-stranded DNA followed by assembly of those oligos into longer dsDNA.[8] Customers often order already-assembled dsDNA from traditional providers, but they can also purchase oligos and assemble them into dsDNA in their own labs, using standard laboratory techniques. Two relatively new technologies can serve as enablers of benchtop DNA synthesis advances: (1) improvements in oligo synthesis made possible by new enzymatic synthesis methods and (2) laboratory robotics, which can make it easier to assemble those oligos into longer dsDNA fragments.

Enabling Technology: Enzymatic Synthesis

The development of enzymatic oligo synthesis methods is a key biotechnology innovation that is driving advances in benchtop DNA synthesis (Box 1).[9] Until very recently, all commercial DNA providers and benchtop DNA synthesis devices used phosphoramidite chemistry for DNA synthesis. However, these methods have very challenging technical requirements and involve highly toxic materials. The chemistry uses anhydrous solvents (i.e., organic solvents with no water), requires reagents to be stored under pressurized argon gas, and produces hazardous waste. To produce high-quality oligos, systems that use this method—including benchtop devices[10]—require skilled technicians to maintain and operate the equipment and laboratory infrastructure to properly store reagents and dispose of waste.

Box 1: Enzymatic Synthesis Versus Phosphoramidite Chemistry

For successful assembly of oligos into longer stretches of dsDNA, it is critical that the oligos have very high sequence fidelity (i.e., very few errors). Phosphoramidite chemistry, the mainstay of DNA synthesis to date, has enabled reliable production of custom-built oligos up to ~120–180 nucleotides in length with sequence fidelity of 99.2%–99.7%. Under ideal synthesis conditions, oligos of up to ~300 nucleotides are possible. Among experts interviewed, opinions were mixed on whether current enzymatic synthesis methods generate oligos as reliable and maintain a sequence fidelity as high as this older method. A few experts predicted that the error rate for enzymatic synthesis would remain sufficiently high that phosphoramidite chemistry will still dominate the DNA synthesis industry in 10 years and possibly longer. Others believe that current enzymatic synthesis methods are comparable to phosphoramidite chemistry in the sequence fidelity of oligos that are produced and that they will eventually surpass that standard, particularly for sequences over 150 nucleotides. For example, the company Camena Biosciences has already claimed reliable enzymatic synthesis of oligos 300 nucleotides in length, which it used to successfully assemble dsDNA that is 2,700 base pairs long.[11] DNA Script,[12] Telesis Bio,[13] and Ansa Biotechnologies[14] have made similar claims for their enzymatic synthesis approaches, reporting very high fidelity oligos. Given ongoing commercial investment and interest in improving enzymatic synthesis (see Table 1), it is likely that these new methods will soon yield oligos of comparable quality and length, if they do not already.

In contrast to these older methods, enzymatic synthesis works in aqueous (water-based) solution and does not generate hazardous waste. In addition to reducing the laboratory infrastructure that is required, next-generation benchtop DNA synthesis devices that use enzymatic synthesis are likely to be much easier to maintain and operate than those that depend on phosphoramidite chemistry, decreasing the level of skill and expertise required of users. For example, DNA Script, the first company to commercialize an enzymatic synthesis-based benchtop DNA synthesis device, claims that its SYNTAX system can be set up in 15 minutes for "plug-and-play automation."[15]

Enabling Technology: Laboratory Automation

To generate longer stretches of dsDNA, oligos are synthesized and joined together. This assembly can be done manually in a laboratory using standard molecular biology techniques but is much easier with laboratory automation (Box 2). Liquid-handling robotics enable automated dsDNA assembly of fragments up to 5,000–7,000 base pairs. Telesis Bio (formerly Codex DNA) developed the BioXp DNA assembly device, which has already demonstrated automated assembly of a dsDNA fragment that is 7,200 base pairs long.[16]

Newer advances in laboratory automation and instrumentation are also contributing to the development of benchtop DNA synthesis devices. These include the use of microfluidics- and chip-based[17] systems that can manipulate tiny amounts of liquid and enable faster, more reliable automation that can conduct many more DNA synthesis and assembly reactions in parallel.

Limitations to Automated DNA Synthesis and Assembly

Given advances in enzymatic synthesis and in laboratory automation, it is technically feasible and likely within 2–5 years that an enzymatic oligo synthesis system will be integrated with DNA assembly robotics to produce an integrated benchtop DNA synthesis and assembly device. Indeed, Telesis Bio, which produces the BioX DNA assembly device, recently announced an enzymatic synthesis platform that they plan to integrate into their device beginning in 2023.[18]

Box 2: Assembly of dsDNA

Gibson Assembly is a commonly used technique for assembly of dsDNA that is highly amenable to automation. This method enables researchers to assemble multiple overlapping oligos (typically ~60 nucleotides) into a longer dsDNA fragment in a single reaction.[19] These dsDNA fragments can then be assembled into increasingly longer dsDNA fragments. For example, ~60 nucleotide oligos can be assembled into ~280 base-pair dsDNA segments, which can in turn be assembled into ~1,200 base-pair dsDNA segments (see Figure 3 on page 21). This technique is seamless, meaning that there are no extra base pairs added between DNA fragments, and can be used with any sequence (e.g., it does not require specific sequences or markers such as restriction enzyme recognition sequences). It is not surprising that Gibson Assembly has already been incorporated into an automated benchtop device; Telesis Bio's BioXp uses this approach to assemble oligos into longer dsDNA.

However, there are significant technical barriers that will limit the capabilities of near-future benchtop DNA synthesis devices (Box 3). This limitation is driven by two factors: (1) imperfect sequence fidelity of initial oligos, which drives a need for quality control sequencing steps for dsDNA assembly, and (2) the need for bacterial or yeast culture to assemble and preserve dsDNA fragments longer than 7,000–10,000 base pairs. Neither quality control sequencing nor bacterial and yeast culture systems are currently amenable to full automation, so they cannot be integrated into near-future automated benchtop devices. Although some study participants believe that these limitations can be overcome, it is improbable in the next 10 years. Therefore, it is likely that fully automated benchtop DNA synthesis devices will be limited to shorter fragments—fewer than 10,000 base pairs—for the foreseeable future.

Box 3: Limiting Factors for Benchtop Capabilities

Sequence Fidelity of Synthesized Oligos

The sequence fidelity of the initial oligos is a key factor that determines the length of dsDNA that can be reliably assembled. Using oligos readily available through current technology (i.e., oligos produced using phosphoramidite chemistry), experts interviewed who are experienced with DNA assembly reported that they generally sequence intermediate assemblies (e.g., ~1,000 base pairs) as well as fully assembled fragments (e.g., ~5,000 base pairs) to most efficiently ensure that the final dsDNA product has the correct sequence and that no stretches of DNA are missing. These quality control sequencing steps require bacterial culture for purification and isolation of the DNA and often depend on laboratory technicians or other personnel to perform sequencing and to analyze sequencing data. As a result, these capabilities are difficult to automate and not likely to be fully integrated into an automated DNA synthesis workflow—or into a benchtop DNA synthesis device—for the foreseeable future.

When very high quality oligos and error correction enzymes (or other error correction approaches such as oligo hybridization[20]) are used, it may be possible to skip a sequencing step (e.g., at an intermediate length of ~1,000 base pairs) and still have a reasonable probability of assembling a longer fragment (~5,000 base pairs) with the correct sequence. Some, though not all, experts interviewed believe that enzymatic synthesis or oligo hybridization methods will enable oligo production with a higher sequence fidelity than that of traditional phosphoramidite chemistry. Although such an advance would lessen the need for sequencing of each intermediate assembly, it is unlikely to eliminate the need for sequencing altogether, particularly for longer dsDNA fragments in excess of 7,000 base pairs.

Need for Bacterial or Yeast Culture for Successful Assembly of Longer dsDNA

Another limitation to the length of dsDNA that could be made by an integrated benchtop DNA synthesis device is that assembly of longer dsDNA fragments (greater than ~7,000 base pairs) or fragments with difficult sequences requires the use of bacteria or yeast to assemble the DNA, which is not amenable to automation. Bacteria are used to help efficiently assemble sequences of up to ~10,000 base pairs, and yeast can assemble dsDNA fragments of up to ~100,000 base pairs and longer in some cases.[21] These cell-based methods make use of cellular DNA processing machinery to assemble DNA and perform error correction and to protect longer fragments of dsDNA from physical damage, such as shearing (i.e., physically breaking DNA into smaller fragments). Successful assembly of dsDNA fragments longer

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Box 3: Limiting Factors for Benchtop Capabilities *(continued)*

than 10,000 base pairs requires, at a minimum, expertise and laboratory infrastructure for working with yeast and access to DNA sequencing capabilities. Moreover, the challenges associated with dsDNA assembly grow exponentially as the length of the dsDNA increases, and overcoming them is likely to require hands-on dsDNA assembly expertise and troubleshooting experience. Assembly of dsDNA that includes sequences that may be toxic to bacteria or yeast—including many viral genomes—may also require knowledge of a wider range of potential strategies for dsDNA assembly.

Some experts posited that benchtop DNA synthesis devices might be able to synthesize gene fragments of 10,000 base pairs and longer within approximately 10 years, given the variety of potential advances in molecular and cell biology. Potential advances in error correction enzymes or cell-free systems may be able to replicate the dsDNA-stabilizing and error correction properties of yeast without the need to culture yeast (though one expert noted that such systems might be very expensive). One expert suggested that advances in commercially available "lab-in-a-box" solutions that seek to provide tools and support for bacterial and yeast culture for lower-resource countries and other customers could be applied to reduce barriers to dsDNA assembly.

Current Benchtop Devices Industry

This overview of the current benchtop device industry provides a snapshot of this rapidly evolving technology. There currently are no commercially available benchtop devices that automate both oligo synthesis and dsDNA assembly, but one company anticipates offering this type of product later this year. Telesis Bio (formerly Codex DNA) currently sells the BioXp, which assembles dsDNA from specialized plates of oligos ordered from the company. As previously discussed, experts believe that an oligo synthesizer could be linked with a dsDNA assembler, similar to the BioXp, to make an integrated device that performs both synthesis and assembly. As anticipated, Telesis Bio recently announced an enzymatic oligo synthesis platform, which it plans to integrate with its DNA assembly device in the near future.[22]

There are also several benchtop devices that synthesize oligos in multiplexed, parallel systems capable of simultaneously producing up to 768 different oligos in a single run. Some of these devices, such as the Dr. Oligo and MerMade systems, use phosphoramidite chemistry (an older, non-enzymatic method for oligo synthesis) and have been available since the 1990s. In June 2021, DNA Script launched the first enzymatic synthesis-based benchtop oligo synthesizer, which can produce up to 96 oligos in parallel.[23]

Table 1 shows companies that are developing or marketing benchtop DNA synthesis devices that perform multiplexed oligo synthesis or DNA assembly, as well as those working to advance enzymatic oligo synthesis technology. DNA synthesis technologies are being developed within a competitive, rapidly evolving market with many active start-ups.[24] It is likely that additional companies not listed here are already raising funds to develop benchtop devices.

Table 1: Benchtop Devices Industry

Maker	Country	Device and year	Description
Biolytic	U.S.	Dr. Oligo 1993	Can synthesize up to 768 oligos in parallel,[a] each up to ~200 nt. Uses phosphoramidite chemistry.
BioAutomation, an LCG company	U.K.	MerMade 1999	Can synthesize up to 192 oligos in parallel,[b] each up to ~200 nt. Uses phosphoramidite chemistry.
Next-generation devices			
Telesis Bio	U.S.	BioXp 2015	Assembles long stretches of dsDNA from specialized plates of oligos that are ordered from the company and has reported the assembly of a 7.2-kb dsDNA fragment.[c] Telesis Bio recently announced an enzymatic synthesis platform and plans to integrate this capability into its BioXp device.[d] Company went public in June 2021.
DNA Script	France	SYNTAX 2021	Can synthesize up to 96 oligos in parallel, each up to 80 nt.[e] DNA Script has also demonstrated enzymatic synthesis of oligos of up to 200 nt.[f]
Evonetix	U.K.	TBA	Developing a benchtop device that uses thermally controlled, chip-based oligo synthesis that is integrated with DNA assembly capabilities.[g] Compatible with phosphoramidite chemistry or enzymatic synthesis.[h]
Nuclera	U.K.	TBA	Developing a benchtop device that uses microfluidics for protein and DNA synthesis.[i]
Enzymatic synthesis technologies			
Molecular Assemblies	U.S.	Developing a Fully Enzymatic Synthesis technology that will be implemented as a service.[j]	
Ansa Biotechnologies	U.S.	Developing enzymatic synthesis to provide DNA synthesis as a service.[k] Has reported synthesis of a 1,005-nt oligo.[l]	
Camena Bioscience	U.K.	Developing enzymatic synthesis to provide DNA synthesis as a service.[m] Has reported oligos of up to 300 nt at 99.9% sequence fidelity.[n]	

Note: kb = kilobase; nt = nucleotides; U.K. = United Kingdom; U.S. = United States; TBA = to be announced.

[a] Biolytic Lab Performance Inc., "Dr. Oligo™ 768XLc: High Throughput Oligo Synthesizer," https://www.biolytic.com/t-dna-rna-oligo-synthesizer-768xlc.aspx.

[b] Biosearch Technologies, "DNA and RNA Oligonucleotide Synthesizers," https://shop.biosearchtech.com/nucleic-acid-chemistry-reagents-and-instruments/dna-and-rna-synthesis-instruments-and-accessories/dna-and-rna-oligonucleotide-synthesizers/c/dna-rna-oligonucleotide-synthesizers.

[c] Telesis Bio, "Telesis Bio Releases Long Gene Fragment Cloning on the BioXp™ System."

[d] Telesis Bio, "SOLA Enzymatic DNA Synthesis Technology."

[e] DNA Script, SYNTAX STX-100 System.

[f] DNA Script, "DNA Script Announces World's First Enzymatic Synthesis of a High-Purity 200-Nucleotide Strand of DNA."

[g] Evonetix, "Our Platform: Third-Generation Gene Synthesis," https://www.evonetix.com/our-platform/.

[h] Evonetix, "Evonetix Demonstrates Novel Enzymatic DNA Synthesis Method."

[i] Nuclera, https://www.nuclera.com/technology/.

[j] Molecular Assemblies, https://molecularassemblies.com/.

[k] Ansa Biotechnologies, https://ansabio.com/.

[l] Ansa Biotechnologies. "Ansa Biotechnologies Announces Successful de novo Synthesis of World's Longest Oligonucleotide at 1005 Bases."

[m] Camena Bioscience, https://www.camenabio.com/about-camena/technology.

[n] Bell et al., "gSynth™: Synthesis and Assembly of Whole Plasmids."

Market Drivers for Benchtop Devices

The market for the new generation of benchtop DNA synthesis devices will determine how widespread these devices become and the range of customers that might use them. The expectations of the customers driving this market, particularly for the level of privacy they anticipate for their ordered DNA sequences, will also shape opportunities for oversight.

There are a wide range of views about the potential market for these devices. Some experts believe that DNA from centralized providers is sufficiently cheap and reliable that it will continue to dominate the dsDNA market for the foreseeable future; as such, benchtop DNA synthesis devices will represent only a small niche. Others argue that more widespread use is a distinct possibility, particularly if and when more user-friendly, enzymatic synthesis-based benchtop devices become cheaper, and if enzymatic synthesis proves as reliable as (or better than) phosphoramidite chemistry for oligo synthesis. Notably, most experts interviewed agree that, for the foreseeable future, these devices would be used primarily in well-resourced laboratories, rather than expanding access to dsDNA for low-resource environments.

Market Driver: Speed

Study participants noted several reasons that a customer might choose to purchase a benchtop DNA synthesis device rather than buy dsDNA from traditional DNA providers and said that **speed** is a critical advantage. For companies or research groups that do many "design-build-test cycles" to develop or optimize engineered biological systems, access to dsDNA can be a key bottleneck. Shipping times of several days can be the slowest step in the process, and benchtop DNA synthesis could eliminate delays. Staffing shortages and other disruptions due to the COVID-19 pandemic created additional delays in processing and shipping of ordered synthetic DNA, which may drive increased interest in benchtop devices.

Market Driver: Confidentiality

Another potential advantage of benchtop DNA synthesis devices is that the user may be able to maintain full **confidentiality** of proprietary DNA sequences. Having a benchtop system that runs entirely on an internal network (i.e., with no connection to the Internet) would further protect sensitive data from unauthorized access. Some study participants believe that this would be a market driver for benchtop devices, pointing to the advantages of privacy, for large pharmaceutical companies working with novel sequences, for example. Experts familiar with the currently available, phosphoramidite chemistry-based benchtop oligo synthesizers—such as the Dr. Oligo and MerMade systems—observed that the device manufacturers do not have visibility into the DNA sequences that are synthesized, and strict confidentiality of the users' sequences is critical to many of those customers. However, other study participants stressed that many potential customers for newer benchtop synthesis devices would not be as concerned about sharing DNA sequences with the manufacturer. They pointed to the current practice of sharing sequences with DNA providers when placing orders and the more open nature of academia.

The market potential for benchtop devices remains unclear, but the level of confidentiality that manufacturers promise to users and build into these devices will have significant implications for biosecurity oversight.

Biosecurity Implications of Benchtop Synthesis Advances

Advances in benchtop synthesis capabilities—along with progress in a broader range of biosciences and biotechnologies—can offer significant potential benefits for human health and medicine, economic development, and pandemic detection and response. However, these advances also raise important questions:

What are the biosecurity implications of potential widespread use of benchtop DNA synthesis devices? How could the biosecurity risk landscape change in the next 2, 5, or 10 years? How urgently must governments, industry, funders, and the broader scientific community act to mitigate any new risks?

Do current or anticipated benchtop synthesis capabilities change the possibilities for generating or enhancing pathogens? Would easier access to dsDNA for nefarious actors meaningfully increase biosecurity risks?

There is a wide range of opinions on how increased availability of benchtop DNA synthesis devices would affect biosecurity in the near future. Most experts interviewed believed that widespread adoption of benchtop DNA synthesis devices would meaningfully reduce a hurdle to illicit use of synthetic dsDNA, increasing the chances that a malicious actor could cause harm. The most commonly cited risk was that benchtop devices might increase the likelihood that a non-state actor or rogue researcher could generate a toxin or pathogen genome from scratch without prior access to the toxin gene or pathogen. A pathogen genome could be infectious on its own or might be used to generate an infectious agent.

A related risk is that a benchtop device may allow synthesis of a DNA sequence (or many variants of a DNA sequence) that can be "dropped into" or otherwise used to alter the genome of an existing pathogen in an effort to make it more pathogenic or resistant to medical countermeasures or to cause some other effect. However, nearly all experts acknowledged that a nefarious actor seeking to generate or otherwise engineer pathogens to cause harm would face significant technical hurdles beyond access to dsDNA. These possibilities and their hurdles are discussed in more detail in the following sections.

In addition to risks related to pathogen engineering, which are the focus of this report, a few experts noted other potential risks associated with widespread availability of benchtop DNA synthesis devices. These potential risks include the possibility that nefarious actors could use synthetic DNA to cause smaller-scale harm, such as an attack on a single person; to self-experiment; or to tamper with sensors, diagnostics, or other biotechnologies. Benchtop DNA synthesis devices could also be used to facilitate engineering of microbial strains that produce toxins or illicit drugs. In addition to direct harms, such attacks or misuse could lead to a backlash or distrust of biotechnologies among the public. Another type of risk cited by study participants is the potential for benchtop devices connected to the Internet to be hacked, leading to disruption of legitimate research or causing synthesis of DNA that is not the intended sequence. While important, these issues are unlikely to have the same level of catastrophic consequences as those related to pathogen engineering.

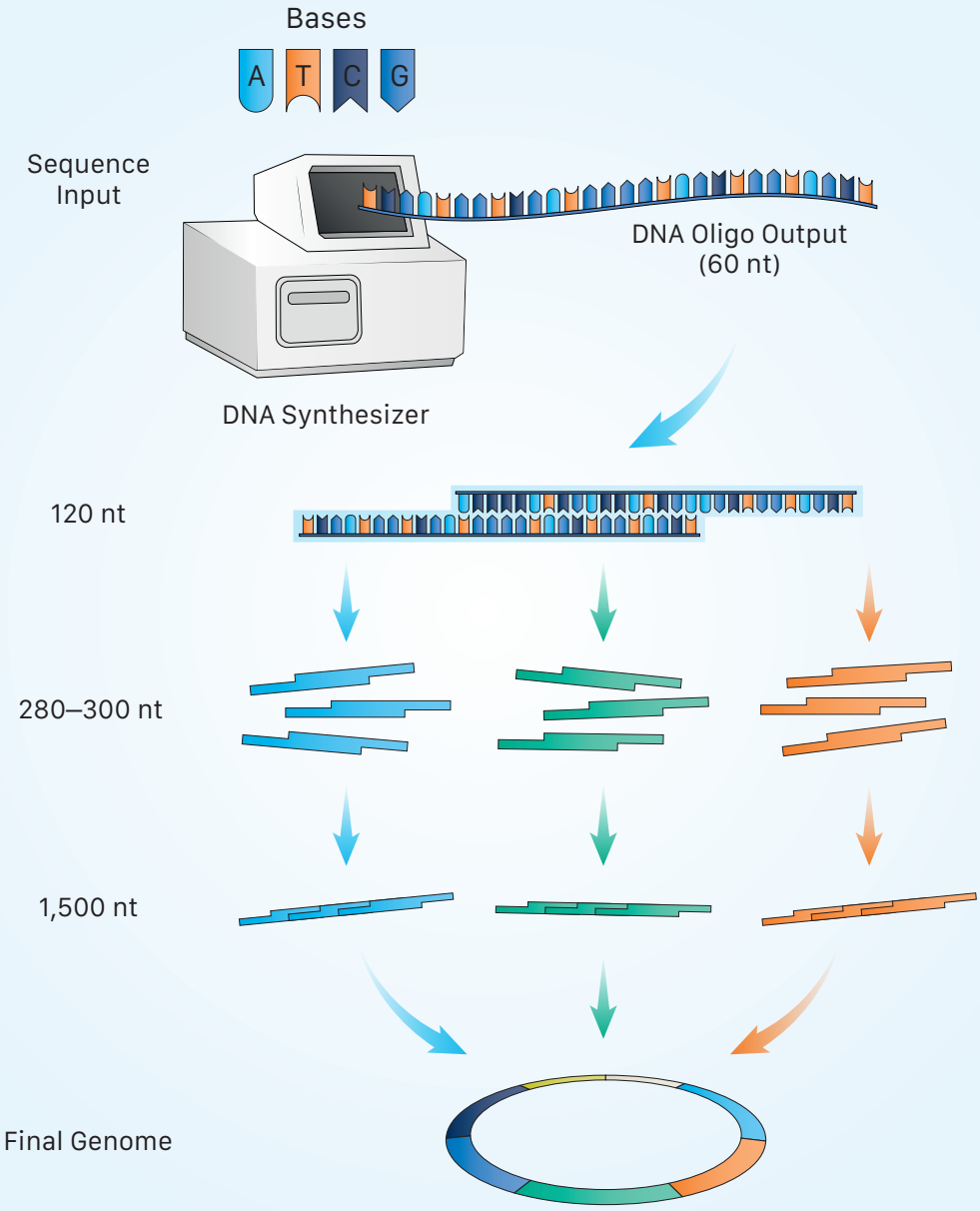
Access to dsDNA by Nefarious Actors

Nearly all experts agreed that availability of next-generation benchtop DNA synthesis devices will make dsDNA synthesis and assembly easier for a wide range of actors, also reducing a hurdle for potential malicious actors. The extent to which next-generation benchtop devices reduce barriers for nefarious actors will depend on how widespread and accessible the devices become and how easy they are to use.

Manual Assembly of dsDNA

A few experts noted that a nefarious actor with some molecular biology expertise would not need a next-generation benchtop DNA synthesis device to generate dsDNA and argued that these new devices therefore do not meaningfully change the biosecurity risk landscape. With access to custom oligos, bad actors could assemble dsDNA at lengths similar to what a next-generation benchtop DNA synthesis device could produce (~5,000–7,000 base pairs) (see Figure 3: Assembling a Genome). They could obtain oligos from a currently available benchtop oligo synthesizer or could order oligos from traditional DNA providers. Such orders are not usually subject to biosecurity screening because oligos and sequences shorter than 200 nucleotides fall outside common practice for sequence screening (see the next chapter, "Benchtop Devices and Biosecurity Governance"). These oligos could then be assembled into longer dsDNA fragments by hand (i.e., using hand-held pipettes, thermal cyclers, and standard molecular biology lab techniques) by using Gibson Assembly

Figure 3: Assembling a Genome



There are several steps in the process to creating a genome from scratch. Often, this process begins with the synthesis of single-stranded DNA oligos about 60 nucleotides (nt) in length. To build a larger fragment, oligos are designed with overlapping, complementary sequences (bases that will pair to each other) so that oligos will anneal (stick together) to form double-stranded DNA. This process of generating longer stretches of dsDNA by annealing sets of overlapping, complementary sequences can be repeated in additional cycles until the final genome is fully assembled. To ensure the correct sequence, this process requires sequencing the assembled DNA at intermediate stages at multiple steps along the way.

or other methods or with assistance from readily available liquid-handling robotics. Life sciences suppliers, including Telesis Bio[25] and New England Biolabs,[26] sell Gibson Assembly kits, and online tools are widely available to assist with protocols and oligo design.[27] These approaches combined with access to sequencing capabilities or services would enable a nefarious actor with some training to produce gene-length dsDNA. Generating longer stretches of dsDNA would remain challenging. (See Box 4 on technical hurdles to assembly of pathogen genomes.)

Although assembly of dsDNA in this way is possible, next-generation benchtop DNA synthesis devices are designed to fully eliminate these steps, including the need for the skills, expertise, and know-how associated with them. Also, as mentioned, a key advantage of these devices will be the speed at which users can access dsDNA, a factor that will benefit rogue actors as well. If and when benchtop devices become widespread, it will become much easier for users at all skill levels to obtain dsDNA.

Opportunities for Misuse of Benchtop DNA Synthesis Devices

Currently and for the near future, the cost of benchtop DNA synthesis devices may remain sufficiently high that they are likely to be used primarily in well-funded research core facilities or otherwise shared among many users. Older, phosphoramidite chemistry-based oligo synthesis devices generally are used in this way in part because they are difficult to operate and require dedicated personnel to ensure production of high-quality oligos. Such an arrangement may limit opportunities for individuals or rogue actors to misuse the devices. If and when benchtop devices become sufficiently low-cost that individuals or small labs can afford them, and sufficiently user-friendly that a non-expert can operate them, opportunities for misuse will expand. The newer, enzymatic synthesis-based benchtop devices promise to be much easier to use, enabling a wider range of users. For example, DNA Script claims that its enzymatic synthesis-based SYNTAX system requires only 15 minutes to set up, and the firm anticipates that benchtop devices will be "as ubiquitous as sequencers and microscopes."[28]

Although these newer devices may reach a broader range of users, a few experts argued that they are more secure than the older, phosphoramidite chemistry-based benchtop devices. Once one of these older-generation devices is installed, there may be limited contact between the user and the manufacturer, reagents are widely available, and there is no visibility into the oligo sequences that are being synthesized. Confidentiality is a key market driver for the older devices.

In contrast, the newer generation of benchtop devices may have constant contact with their manufacturers to ensure accurate synthesis of each oligo and assembly into dsDNA. Both DNA Script's SYNTAX system, which synthesizes oligos, and Telesis Bio's BioXp, which assembles oligos into dsDNA, require that the manufacturer have access to the ordered DNA sequences, providing an opportunity to conduct sequence screening prior to synthesis. Devices that integrate oligo synthesis with dsDNA assembly, anticipated in the near future, may have similar requirements. Furthermore, several study participants noted that devices using enzymatic synthesis may require patented cartridges with enzymes and other reagents, which will help ensure an ongoing relationship between customers and device manufacturers. Some, but not all, experts familiar with these newer systems agreed that benchtop device manufacturers are anticipating business models that include ongoing contact with users, including access to ordered DNA sequences. It remains unclear whether customers for these devices will demand more confidentiality than manufacturers currently expect.

Pathways to Risk: Benchtop DNA Synthesis Devices and Pathogen Engineering

Most experts agree that availability of benchtop DNA synthesis devices could lower some hurdles to pathogen synthesis and engineering by facilitating easier access to dsDNA. To better understand this risk, it is important to determine the hurdles a nefarious actor might face in undertaking such a project and to evaluate the ways in which easier access to dsDNA might reduce them. This project focused on three strategies that a nefarious actor might attempt in order to inflict significant harm, including (1) assembling a full pathogen genome—i.e., generating DNA that encodes the pathogen's full genetic blueprint; (2) "booting up" a pathogen—i.e., creating a functional pathogen from the DNA that encodes its genetic blueprint; and (3) altering or enhancing the properties of a pathogen beyond those found in nature, for example, by making it more transmissible or virulent and/or resistant to medical countermeasures. (See Box 4 on technical hurdles to assembly of pathogen genomes.) This analysis is primarily focused on viral pathogens because they are the most likely to spread rapidly and cause catastrophic harm and because they have relatively small genomes compared to bacterial or eukaryotic pathogens.

Each of these pathways to risk poses significant technical hurdles for nefarious actors, and access to dsDNA may help overcome some but not all of them. These hurdles include:

- **Synthesis and assembly of pathogen genomes—**For de novo assembly of most pathogen genomes, an individual or group would need to assemble long fragments of dsDNA (greater than 10,000 base pairs). Benchtop DNA synthesis devices are likely to lower, but not eliminate, this hurdle.
- **Booting up infectious agents from dsDNA encoding pathogen genomes—**For most pathogens, booting up a functional pathogen from a dsDNA genetic blueprint requires laboratory infrastructure and agent-specific expertise. Benchtop DNA synthesis devices are not likely to reduce this hurdle.
- **Altering or enhancing pathogen genomes—**Challenges to the intentional design or alteration of a pathogen's characteristics include scientific knowledge gaps on how genomic alterations affect a pathogen's properties, as well as scientific uncertainties about the complex inner workings of biological systems. Benchtop DNA synthesis devices may provide easier access to DNA fragments (including many different variants of DNA sequences) for use in such projects but are unlikely to significantly reduce this hurdle.

To overcome the range of technical hurdles outlined, an individual or group would likely need a range of skills, expertise, and laboratory infrastructure. A few experts expressed the opinion that a person or group with the capacity to reliably assemble viral genomes and boot up infectious viruses would not consider access to dsDNA to be a significant obstacle, regardless of the availability of benchtop DNA synthesis devices. However, experts also pointed out that some pathogens pose fewer pathogen engineering challenges than others, and in these cases, access to dsDNA could be particularly helpful to a malicious actor. Furthermore, it is likely that each of these hurdles will continue to decline over time as scientific advances by legitimate researchers add additional tools and knowledge to the public domain.

Box 4: Technical Hurdles to Pathogen Engineering

1. Pathogen Genome Assembly

The most capable near-future benchtop DNA synthesis devices are likely to produce stretches of dsDNA up to approximately 7,000 base pairs. There are a few viral genomes that are shorter than 7,000 base pairs, and a benchtop device could eliminate barriers to obtaining these genomes. However, most viral genomes are between 10,000 and 200,000 base pairs, and bacterial genomes are longer than 1 million base pairs. A nefarious actor seeking to generate whole pathogen genomes at these lengths from scratch would still face significant hurdles. As noted earlier, reliable assembly of dsDNA fragments longer than ~7,000–10,000 base pairs requires working with bacteria and, for longer sequences, yeast to take advantage of their DNA-processing capabilities (such as DNA assembly and error correction) and for stability of the dsDNA. Also, many viral genomes contain DNA sequences that are toxic to bacteria and yeast, which can make assembly of certain portions of viral genomes particularly difficult and may require alternative methods.[29]

Experts familiar with assembly of viral genomes argued that an individual or group with basic molecular biology skills (including bacterial and yeast culture) could likely assemble a viral genome that was 10,000–12,000 base pairs. Assembly of larger viral genomes (up to 30,000 base pairs) requires additional know-how, including virus-specific expertise and troubleshooting capabilities, and is thus more likely to be a group effort. Synthesis of dsDNA viral genomes of 100,000–200,000 base pairs is very difficult and requires extensive DNA assembly expertise, additional virus-specific knowledge of problematic sequences and genomic structural elements, and a sustained effort.[30] Assembly of bacterial genomes (larger than 1 million base pairs) remains unattainable except for a single proof of principle by a team of leading researchers in 2010.[31]

For many pathogens, isolating samples from the environment would be easier than synthesizing their genomes from scratch. Still, a few experts pointed to scientific publications and ongoing advances that may reduce hurdles to pathogen genome synthesis and assembly in the future.

2. Booting Up Infectious Agents from dsDNA Genomes

In most cases, nefarious actors would face obstacles to producing a functional infectious agent even if they already had the full dsDNA pathogen genome. Booting up a virus from a dsDNA genome can be challenging, though the level of difficulty depends on the type of virus.[32] For some viruses, a dsDNA genome is infectious on its own, so there are few hurdles to generating an infectious agent. In these cases, transfecting mammalian cells with the dsDNA genome (i.e., driving the cells to take up and express the DNA) is all that is required. However, most viruses require additional genes or helper viruses to provide essential viral proteins not found in the host cell, and additional expertise is often required in this step (see Figure 4: Booting Up a Viral Genome).

There have been advances over many years in the scientific understanding of what is needed to boot up different types of viruses, and doing so requires virus-specific expertise. At a minimum, generation of an infectious agent from a dsDNA genome requires the laboratory skills and infrastructure for molecular biology and mammalian cell culture. Other types of expertise, such as virology, may also be needed, as well as laboratory infrastructure including biosafety cabinets, autoclaves, and incubators. Scaling up production would require an even broader set of skills, personnel, and facilities, as would reliable testing of viruses for the intended effects.

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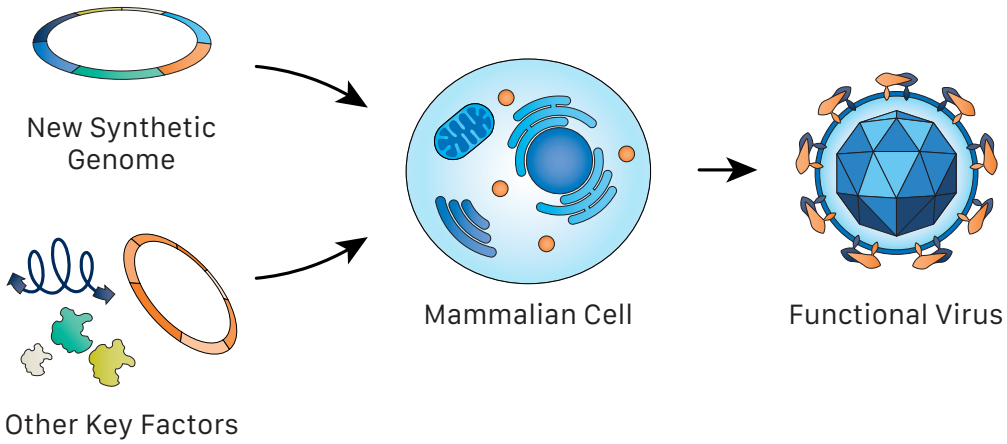
Box 4: Technical Hurdles to Pathogen Engineering *(continued)*

Figure 4: Booting Up a Viral Genome



To generate an infectious agent from a dsDNA genome, the genome must be inserted into and expressed by a host cell. For many viruses, other key factors (such as helper viruses, transcription factors, or viral proteins) must be inserted in a compatible host cell alongside the genome itself. This allows the viral lifecycle to begin, coopting the cellular machinery of the cell, and creating copies of the viral genome and proteins before fully assembled, infectious viral particles exit the cell.

In their work to understand and combat infectious disease, scientists continue to improve methods for booting up infectious viruses, making them easier and more applicable to a wider range of viruses. These advances, when published, will also decrease the hurdles for nefarious actors. A few experts expressed concern that the ability to boot up viruses might someday become broadly accessible or even available as a kit. Still, most experts argued that in most cases, generating an infectious agent from viral genomes would continue to be challenging and would require virus-specific expertise and training for the foreseeable future. Availability of benchtop DNA synthesis devices is not likely to reduce this technical hurdle.

3. Altering or Enhancing Pathogen Genomes

It is possible that nefarious actors could use a benchtop DNA synthesis device to generate dsDNA fragments (or even shorter oligos) that could be used to change the characteristics of a virus they already have in hand by adding or substituting DNA sequences (see Figure 5: Editing a Genome). For this scenario, several experts emphasized that there would be significant challenges due to a lack of scientific knowledge on what genes to add or which sequences to alter, as well as the inherent uncertainty about the complex inner workings of biological systems. They argued that it would be difficult to design changes to complex traits such as transmissibility or virulence and that changes to a viral genome would be more likely to disable it than to create an enhanced viral pathogen. They noted that an individual or group seeking to enhance a pathogen with characteristics more dangerous than those found in nature—without prior knowledge of pathogenicity factors from the scientific literature or tacit knowledge from experience—would require luck to be successful. Attempts to alter or enhance viral genomes would also require overcoming other hurdles associated with working with viruses, including booting up an infectious agent from dsDNA genomes, as previously discussed. The challenge of discovering novel variants with altered or enhanced characteristics is underscored by the extensive resources and expertise legitimate researchers require to conduct such research.

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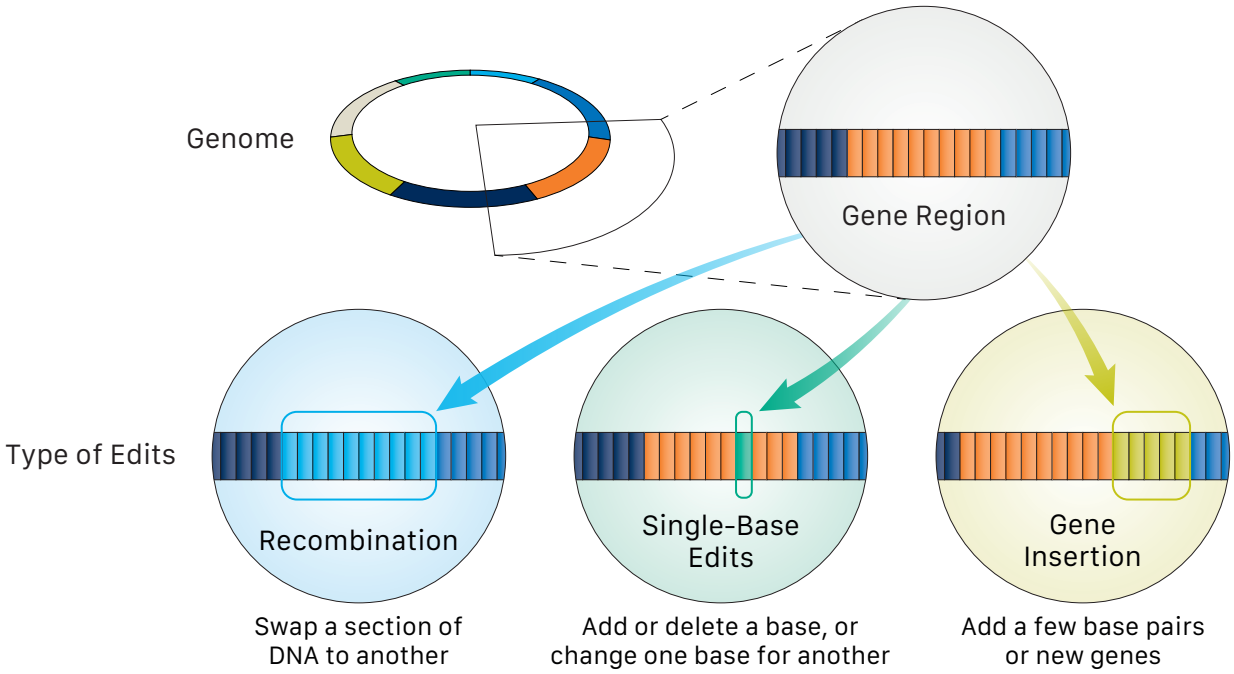
Box 4: Technical Hurdles to Pathogen Engineering *(continued)*

Figure 5: Editing a Genome



Changing the sequence of a genome can alter the characteristics of an organism. These modifications can be as small as altering a single base through addition, deletion, or substitution, or as large as swapping out or adding entirely novel sections of genetic code. These modifications can occur through random mutation, or be achieved through classical biochemistry techniques, or using tools like CRISPR-Cas.

On the other hand, a few experts did see significant risk in the possibility of creating an enhanced pathogen and noted that there already is information in the public domain that could inform such an effort. They argued that viruses, particularly those with larger genomes, and bacterial pathogens (or even non-pathogenic bacteria) could be altered in a way that would make them more harmful than variants found in nature, for example by adding genes to circumvent medical countermeasures. Also, legitimate research, particularly "gain-of-function" research on dangerous pathogens, often uncovers mutations in a pathogen genome that could meaningfully alter its characteristics. In addition to providing oligos and dsDNA for such use, the availability of a benchtop DNA synthesis device could also make it easier to try many variants of a gene or DNA sequence in a viral or bacterial genome to test for those with the intended traits. Such an approach would be plausibly feasible in a well-resourced lab.

In some cases, nefarious actors would face trade-offs in the types of hurdles they would have to overcome. For example, as discussed previously, viruses with smaller genomes are much easier to assemble de novo than those that have larger genomes. However, viruses with small genomes may be more difficult to alter or enhance. Experts in virology noted that smaller viruses are less able to accommodate significant additions to their genomes because such additions disable the viruses by disrupting their highly compact physical structure. Also, very small viral genomes can be very complex (e.g., with overlapping genes), making purposeful engineering especially difficult. A nefarious actor would have to balance these types of considerations in any attempt at pathogen engineering.

Benchtop Devices and Biosecurity Governance

In the near future, widespread availability of user-friendly benchtop DNA synthesis devices may increase biosecurity risks. This chapter will focus on actions that industry, governments, and other key stakeholders can take to reduce these risks. Specifically, this chapter will address the following key questions:

- **What types of oversight and governance measures would be most effective for safeguarding benchtop DNA synthesis devices?**
- **What responsibilities should device manufacturers have? What responsibilities should governments have, and what role should other stakeholders play?**

Bioscience and biosecurity experts hold a wide range of opinions and perspectives on how best to reduce risks related to widespread availability of benchtop DNA synthesis devices, and most agreed that biosecurity precautions could meaningfully reduce risks without unduly limiting legitimate research. However, one common theme is that there is no feasible oversight mechanism or policy that will eliminate all risk; the approaches described in this chapter might be better characterized as "speed bumps" to limit or slow the actions of a nefarious actor.

A couple of the experts consulted believe that the biosecurity risks related to this new generation of benchtop DNA synthesis devices are significant enough that the devices should not be allowed to become established in the marketplace. One idea to prevent further development of a market for benchtop devices is to support centralized DNA providers with direct subsidies or investment in DNA synthesis and assembly technologies for centralized providers. Alternatively, governments or outside parties could directly offer high-quality dsDNA to legitimate researchers at very low costs to decrease demand for commercial dsDNA.

However, most study participants agreed that efforts to safeguard benchtop devices should extend and adapt biosecurity provisions followed by traditional DNA providers to encompass this new part of the market. The International Gene Synthesis Consortium (IGSC)[33]—a group of DNA synthesis providers that includes commercial and non-profit providers from across Asia, Europe, and North America—has set standards for voluntary biosecurity screening practices that are consistent with guidance issued in 2010 by the U.S. government. In the United States, the U.S. Department of Health and Human Services (HHS) Screening Framework Guidance provides recommendations for DNA providers to conduct screening for orders of dsDNA that includes customer screening to determine their legitimacy as well as sequence screening of the ordered dsDNA. Updated guidance from the United States was released for public comment in 2022 but has not yet been finalized (Box 5). There is currently no government in the world that requires this type of screening. Although there are ongoing discussions about how to improve the U.S. government's guidance, many experts agreed with the overarching approach in which device manufacturers take the lead in providing biosecurity oversight. Many of the ideas described in this chapter are based on this industry-led approach. However, a broad range of stakeholders, including governments, funders, the scientific community, and civil society, should play a role in oversight of benchtop devices.

Customer Screening: Ensuring Legitimacy of Users

Nearly every expert interviewed emphasized the need to ensure that the end users of benchtop DNA synthesis devices are legitimate, and they offered a wide range of ideas and views on how to do so. A critical challenge for any customer screening method is that a nefarious actor with sufficient expertise, training, and laboratory infrastructure to overcome hurdles related to working with dangerous pathogens may be indistinguishable from a legitimate researcher and may be part of a legitimate institution or community. In addition to customer screening by device manufacturers or the possibility of using third-party customer verification strategies, discussed later, some experts argued that institutional oversight of benchtop device users—e.g., through institutional biosafety committees—could provide more effective oversight because they are closer to and more familiar with the relevant individuals than device manufacturers or third parties.

Customer Screening by Benchtop Device Manufacturers

Customer screening by the product developer is one potentially effective approach to ensure customer legitimacy. All industry-aligned experts who participated in our project were familiar with

Box 5: U.S. Government Screening Framework Guidance

In 2010, to help prevent illicit use of pathogen or toxin DNA, the U.S. government issued the HHS Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA.[34] This guidance provides a framework and recommended practices that have been very influential among DNA providers. It recommends that these companies screen customers to ensure that they are legitimate users of synthetic dsDNA and screen sequences to determine whether they match DNA sequences belonging to pathogens or toxins on regulated pathogen lists. If sequences match pathogen or toxin DNA, the company should conduct follow-up screening to determine whether the customer has a legitimate use for them. Over the years, there has been ongoing discussion about how to improve the guidance[35] and frameworks to support adherence.[36]

In April 2022, the U.S. government published a revised Screening Framework Guidance document for public review and comment.[37] The revision includes recommendations specific to manufacturers of benchtop synthesis devices that follow a framework—with customer screening and sequence screening—similar to the one developed for traditional DNA providers. The revised guidance also makes other updates, including more specificity in its customer screening recommendations and changes to the criteria for sequence screening. The 2010 guidance stated that only dsDNA sequences over 200 nucleotides long should be screened and that sequences requiring follow-up included only those that match sequences found in regulated pathogens or toxins. The 2022 guidance includes both double- and single-stranded DNA and reduces the cut-off for screening to sequences over 50 nucleotides (and as low as 20 nucleotides in some cases). It also expands the types of sequences that require additional scrutiny beyond regulated pathogens and toxins to any DNA sequences that may constitute a risk. This revised Screening Framework Guidance generated extensive discussion and feedback[38] and is likely to incorporate additional changes in the future.

lists, maintained by governments, of individuals or countries that should be denied products and services. Many DNA providers, including members of the IGSC, go beyond these lists to ensure that all customers are legitimate users of dsDNA, for example by requiring an institutional affiliation. The revised Screening Framework Guidance from the U.S. government also recommends that manufacturers of benchtop DNA synthesis devices screen customers to ensure legitimacy, and many experts agree that this is a reasonable approach.

However, making a determination about who is a legitimate user can be challenging and requires resources. Relying solely on companies will lead to an uneven commitment to screening and inconsistent outcomes. DNA providers who have performed this type of customer screening have already encountered challenges, and stronger incentives to conduct such screening may help address them.

Customer Screening by a Third Party

Licensing or certification for users of benchtop DNA synthesis devices (or, more broadly, for legitimate customers of life sciences products) is another potentially effective approach to ensuring customer legitimacy. In this case, potential users would obtain a license or certification by applying to a government or a third party and by undergoing some screening process. Benchtop device manufacturers could then require that customers have a license before selling a device to them. This approach would depend on governments or a third party to standardize a screening method and offer

licenses or certifications. However, currently there is no consensus on what constitutes a legitimate user and there are no entities that offer such a service. Additionally, although this system might provide a benefit to companies, it is not clear whether life sciences practitioners would support this approach because of concerns that it may limit access to products that should be readily available.

Challenges to Safeguarding the Secondhand Market for Benchtop Devices

Many experts raised concerns about a potential secondhand market for benchtop DNA synthesis devices, which may complicate customer screening efforts. If manufacturers do not put in place provisions to ensure that secondhand device owners are screened, that could constitute a significant gap in biosecurity safeguards for benchtop synthesis devices.

As previously discussed, there are key differences between oligo synthesis devices already on the market and those anticipated in the near future, which may shape the secondhand market for each of these systems. The secondhand market for older, phosphoramidite chemistry-based benchtop oligo synthesizers is somewhat constrained by the relative difficulty of operating and maintaining these devices. While these devices can be refurbished or reinstalled and use reagents that are available from a wide variety of sources, experts familiar with their manufacturers reported that they generally maintain relationships with customers to provide troubleshooting, maintenance, and repairs.

Likewise, companies developing or marketing newer benchtop DNA synthesis devices also anticipate ongoing communication with customers, which will affect the secondhand market, but for different reasons. Some manufacturers plan to maintain connectivity to the device for each oligo synthesized and each dsDNA fragment assembled, for example by using a cloud-based system. Some next-generation benchtop devices may also require patented cartridges provided only by the manufacturer. These types of approaches, if successful, may help ensure that the device is not transferred to a third party without notice. Still, it will be important to track the evolution of benchtop device technologies and the market over time, and any customer screening framework—either manufacturer based or through third-party certification—will need to account for potential secondhand use.

Sequence Screening: Limiting Access to Pathogen or Toxin DNA

Most dsDNA 200 nucleotides or longer that is sold by commercial DNA providers is screened to determine whether its sequence matches pathogen or toxin DNA. The revised Screening Framework Guidance from the U.S. government in April 2022 (Box 5) recommends that DNA providers screen DNA sequences that are 50 nucleotides or longer (or sequences as short as 20 nucleotides in some cases), but this guidance is not yet finalized, and it is not yet clear if sequence screening at this length will be widely adopted. If a DNA sequence matches pathogen or toxin DNA, then DNA providers are expected to follow up with customers to determine whether they have a legitimate use for it. Most experts interviewed argued that similar screening protocols should be incorporated into the workflow of benchtop DNA synthesis devices that produce similar DNA. However, a few experts noted that implementing sequence screening precautions might be difficult to do well and could slow legitimate research. The potential for hacking or otherwise bypassing screening could further limit its value.

Methods for Incorporating Sequence Screening into Benchtop Devices

Study participants discussed two potential approaches to sequence screening on benchtop

devices: (1) a "phone home" approach in which the device sends ordered sequences to the manufacturer or to a secure, cloud-based server, where sequence screening can be performed, and (2) a distributed approach to screening that is conducted locally and automatically by the device (or a local server). Each of these approaches has advantages and disadvantages.

For devices using the centralized phone-home screening approach, each sequence would be screened by the manufacturer prior to its synthesis, and a match to pathogen or toxin DNA would require that the manufacturer conduct follow-up screening to determine whether the customer has a legitimate use for it. This type of system would be consistent with the revised Screening Framework Guidance. It is also consistent with current practices for Telesis Bio's BioXp DNA assembly device. When customers order oligos to be assembled by BioXp, Telesis Bio screens the sequence and conducts follow-up screening if necessary.

This centralized sequence screening approach by benchtop device companies would pose many of the same challenges that traditional DNA providers have already experienced.[39] Additionally, confidentiality of the users' DNA sequences may be a key market driver for benchtop DNA synthesis devices. Absent strong incentives, some manufacturers may choose to make assurances to customers that their DNA sequences will remain entirely confidential and without oversight by the manufacturer.

For devices that utilize a distributed, automatic sequence screening approach on the apparatus itself (or on a local server), the manufacturer could periodically check the device for flagged orders, or the device could be programmed to not synthesize sequences that match pathogen or toxin DNA without specific override instructions. Such an approach would more effectively ensure confidentiality of DNA sequences and could be used even if the device remains unconnected to the Internet most of the time. Local oversight, for example by a biosafety officer or an institutional biosafety committee working with the manufacturer, could provide additional confidence that effective sequence screening is being conducted. However, it remains unclear whether the next generation of benchtop devices will have sufficiently powerful computers to conduct sequence screening without being connected to external servers. Additionally, there is no available sequence screening mechanism that is suitable for this type of automated use. However, multiple projects that intend to address this need—including SecureDNA[40] and the international Common Mechanism for DNA Synthesis Screening under the NTI-WEF Technical Consortium—are under development.[41]

Challenges Related to Hacking or Bypassing Biosecurity Screening

For the sequence screening approaches discussed above, hacking to circumvent sequence screening is a critical concern—either cyber hacking to interfere with external screening approaches or altering the device to override local screening and controls. This problem is particularly acute for devices with no regular contact with the manufacturer or other external servers; altering a device to delete or bypass security screening may be simple for anyone with sufficient computer programming skills. Connections between the device and the manufacturer or cloud-based servers may also be relatively easy to "spoof," enabling actors to disrupt or falsify communication with sequence screening servers. Study participants noted that researchers might attempt to circumvent screening even without serious nefarious intent; a graduate student or postdoctoral researcher who feels inconvenienced by slight delays or occasional follow-up questions from the manufacturer may feel justified in doing so.

Still, some type of oversight for each synthesized sequence would provide a speed bump to a nefarious actor, adding hacking as one more skill an individual or small group would need to employ.

Furthermore, sequence screening would also help prevent accidental misuse of synthetic DNA by raising a flag for potentially dangerous pathogen or toxin DNA sequences.

Incentives for Oversight of Benchtop DNA Synthesis Devices

Many of the screening practices described above rely on benchtop device manufacturers to bear the burden of reducing the risks that arise from their devices. Such an industry-led framework is consistent with how DNA providers have overseen the use of dsDNA to date. Although many DNA providers conduct screening, not all choose to do so because it can be costly. The experience of traditional DNA providers demonstrates the need for appropriate resources and incentives for benchtop device companies to incorporate robust biosecurity oversight measures and controls.

Liability can be a powerful incentive for more-secure devices or better practices by the manufacturers, and a few experts suggested that device manufacturers be held accountable if their products are misused. One expert suggested revisiting the Terrorism Risk Insurance Act, which limits the liability that a company can face in the United States due to an act of terrorism,[42] so benchtop device manufacturers could incur the full extent of liability if their products are misused for nefarious purposes. However, such an approach would be controversial, particularly among industry stakeholders. Insurance mechanisms that recognize and incentivize biosecurity best practices by benchtop device manufacturers could also be used to provide additional financial inducements for security measures.

Role of Governments in Establishing Incentives

There is a range of views on the role of governments in providing incentives to mitigate risks related to benchtop DNA synthesis devices. Most participants agreed that governments should develop guidance to guard against exploitation of devices by malicious actors and accidental misuse. However, study participants were divided on the question of whether potential oversight mechanisms should be purely voluntary—as is the case in the 2010 HHS Screening Framework Guidance and its recent revision—or required by regulation. A view commonly held among industry-aligned experts was that regulation would provide the benefit of helping to level the playing field by requiring all competitors to implement similar biosecurity oversight procedures rather than offering a voluntary system in which companies can gain an advantage by skirting the recommended processes.

However, establishing regulations would require governments to specify details of compliance, such as the types of technologies regulated (Box 6), information reported by manufacturers (and to whom), who is a legitimate customer, and which sequences should be included in screening algorithms. Given the challenges companies have already faced in making reasonable determinations, governments may also struggle to parse through gray areas and establish such rules in the near future. Furthermore, governments have been hesitant to provide specific information about DNA sequences of concern, fearing that such information could be misused. Also, regulations in a single country may push less scrupulous manufacturers or users to countries or regions with less oversight. To avoid this potential "race to the bottom" dynamic, it may be more effective to pursue standards that are developed, enforced, and practiced internationally.

Absent regulation, governments could also explore the possibility of encouraging adherence to voluntary guidance. For example, they could use research funding to support benchtop device companies that adopt biosecurity best practices by requiring entities that receive government funds to purchase devices only from those companies. The state of California considered a

Box 6: What Should Be Regulated?

The experts interviewed expressed a range of views about regulatory oversight of benchtop synthesis devices, from skepticism about this approach to the belief that all benchtop devices should be regulated. Decisions about whether to regulate benchtop devices and, if so, how, will be driven by practical considerations as well as the need to balance the biosecurity risks with the device benefits. Given the rapid pace of technology development, it will be important for any regulatory framework to maintain flexibility and to incorporate strategies for regular updates to regulatory requirements.

To capture many near-future benchtop devices, multiple experts suggested that governments could issue regulations that cover benchtop devices capable of reliably synthesizing or assembling DNAs of 200 nucleotides or longer. This length would be consistent with common voluntary sequence screening practices among traditional DNA providers. Many developers of benchtop devices already anticipate incorporating additional biosecurity practices for sequences 200 nucleotides or longer.

A key advantage of this approach is that benchtop devices and traditional DNA providers would be held to the same standard for sequence screening, but it is possible that this standard could change. The U.S. government's April 2022 revised Screening Framework Guidance reduces the length of sequences that are recommended for screening from 200 nucleotides and longer to 50 nucleotides (or as low as 20 nucleotides in some cases). This revision was open for public comment in 2022, and it is not yet clear whether 50 nucleotides will become a standard length for DNA sequence screening. If it does, then regulations for benchtop devices capable of synthesizing DNA of 50 nucleotides may be appropriate.

Regulations that capture fewer benchtop DNA synthesis devices—combined with voluntary guidance for devices that are not covered by regulations—could still limit biosecurity risks. For example, for these devices, governments could establish regulations consistent with export controls; Australia Group member countries currently control devices that can generate high-quality DNA of 1,500 or more base pairs.

bill that would implement such a system,[43] but the bill was ultimately vetoed over concerns about adequate financing and about creating a state-level policy to address a broader national and international issue.

Export control is another tool for government oversight, and benchtop DNA synthesis devices already are listed as controlled technologies. For example, member countries of the Australia Group export control regime have agreed to control export of "Nucleic Acid Assemblers and Synthesizers, which are partly or entirely automated and designed to generate continuous nucleic acids greater than 1.5 kilobases in length with error rates of less than 5% in a single run."[44] A benchtop device that combines oligo synthesis with simple DNA assembly (a near-term possibility, as discussed previously) would fall under these rules. Telesis Bio's BioXp, which assembles DNA from oligos supplied by the company, already meets the control criteria. More recently, the U.S. government published a rule in 2021 that places controls on software that enables assembly of dsDNA from oligos.[45] Experts interviewed had mixed views as to whether this rule would be enforceable and effective, with some expressing concern that this type of software could be collaboratively developed and/or openly distributed, making controls difficult.

Recommendations

Within the next 2–5 years, commercially available benchtop DNA synthesis devices are likely to have the capability to provide users—including those with limited molecular biology skills—easier access to oligos and to dsDNA up to 7,000 base pairs long. To date, industry has taken the lead on safeguarding benchtop devices and preventing their misuse, including by participation in forums such as the IGSC[46] and by voluntarily developing new strategies and technology solutions to safeguard these devices. Policymakers within government should also work to ensure that benchtop DNA synthesis devices have appropriate oversight and safeguards.

While the authors of this report are not aware of feasible options that would eliminate all risk, a range of actors working in concert—including benchtop DNA synthesis device manufacturers, national governments, private organizations, and the scientific research community—can raise hurdles against malicious misuse of these technologies. The U.S. government's revised Screening Framework Guidance is a good first step in setting standards and expectations for manufacturers of these devices, but more work needs to be done to ensure a coherent approach internationally.

The findings of this report were based on extensive research and interviews with a wide range of experts and stakeholders. The following recommendations were developed by the authors, and they do not necessarily represent the views of the experts who participated in this project.

Benchtop synthesis device manufacturers should conduct rigorous customer screening for those who want to purchase or use their devices.

- **Benchtop DNA synthesis device manufacturers should screen customers prior to selling the devices to ensure that each customer is a legitimate user.**
  - » Screening should require documentation to ensure that the customer is associated with a legitimate research or industry organization.
  - » If a benchtop device will be used without direct manufacturer oversight—i.e., if a phone-home approach for screening each sequence prior to synthesis is not feasible—customer screening should be particularly rigorous. The process should ensure, for example, that the customer has onsite biosafety oversight, such as an institutional biosafety committee or biosafety officer with training and resources to prevent illicit synthesis of pathogen or toxin DNA.
  - » Manufacturers should consider using a third-party certification system, if available, that verifies customer legitimacy, particularly if a benchtop device will be used without direct manufacturer oversight of sequences.

- **Customer screening by benchtop DNA synthesis device manufacturers should include ongoing verification of end users.**
  - » Manufacturers should require device users to verify their identity periodically, with tools such as two-factor authentication, in order to continue using the device.
  - » To ensure that ongoing verification of end users is effective, manufacturers should develop strategies to control critical supplies and services needed to keep the device running.
  - » To secure the secondhand market for benchtop devices, manufacturers should conduct full customer screening of new owners before they are allowed to operate the device.

Benchtop synthesis device manufacturers should ensure that each DNA fragment produced by the device undergoes rigorous sequence screening.

- **Manufacturers should conduct sequence screening using a direct oversight approach in which the benchtop device phones home, where feasible.**
  - » This approach could include direct communication between the device and the manufacturer or a cloud-based system in which the manufacturer is notified of screening results. Each sequence should be screened and cleared by the manufacturer prior to synthesis. If a sequence is a hit (i.e., if it matches pathogen or toxin DNA or might endow or enhance pathogenicity), then the manufacturer should follow up with customers to determine whether they have a legitimate reason to have it.
  - » If a phone-home approach is not feasible, then the manufacturer should require that each sequence is screened locally, either on the device itself or on local servers prior to synthesis. In this case, the manufacturer should ensure that the device is used at a legitimate institution that has onsite biosafety oversight, such as an institutional biosafety committee or biosafety officer with training and resources to prevent illicit synthesis of pathogen or toxin DNA. The manufacturer should require periodic reporting of sequence screening results.
  - » Manufacturers should design sequence screening practices to reduce the risk of hacking or circumvention of sequence screening. For example, cybersecurity best practices should be followed, and for built-in screening systems, manufacturers should use tamper-proof or tamper-evident devices that are checked periodically.

- **Device manufacturers should follow DNA sequence screening standards that at least match a minimum standard used by traditional DNA providers.**
  - » Current practice by leading DNA providers is to conduct sequence screening on dsDNA of 200 or more nucleotides, and screening is designed to raise flags for ordered DNA sequences that are found in regulated pathogens and/or that endow or enhance pathogenicity.
  - » Device manufacturers should work with traditional DNA providers and others toward more rigorous sequence screening standards. For example, methods should be developed to screen both single-stranded and dsDNA, DNA shorter than 200 nucleotides, and oligos that are synthesized in parallel specifically for dsDNA assembly.

Governments should provide clear guidelines, strong incentives, and, in some cases, regulations for benchtop device manufacturers to incorporate robust customer and sequence screening.

- **Governments in countries around the world should develop voluntary guidance to set clear expectations regarding customer and sequence screening practices by benchtop DNA synthesis device manufacturers.**
  - » Guidance for these devices should define baseline standards that build on current recommendations for traditional DNA providers, which include both customer screening to check for legitimacy and sequence screening.
  - » Guidance should encourage benchtop device manufacturers to work with DNA providers to develop more rigorous sequence screening practices, as described above.

- **Within 2 years, national governments should plan to implement regulatory requirements for selling or operating benchtop DNA synthesis devices within their borders that are capable of automatically synthesizing and assembling DNA to generate dsDNA with high sequence fidelity at a length of 200 nucleotides or more.**
  - » Such regulations would be consistent with common practice for biosecurity screening of dsDNA of this length.
  - » As an alternative, governments could opt to harmonize regulatory requirements with export rules already in place under the Australia Group export regime, which includes controls on benchtop devices capable of synthesizing or assembling DNA fragments with high sequence fidelity at lengths greater than 1,500 base pairs.
  - » Regulations should include requirements that the device manufacturers meet standards for customer and sequence screening practices. To ensure that regulatory requirements are enforceable, governments should immediately begin to develop a certification process with explicit criteria. For example, for customer screening, governments should list criteria and documentation that would allow a customer or institution to be considered a legitimate user. For sequence screening, governments should provide a specific set of DNA sequences that should be flagged by screening procedures, as well as standards for screening algorithms. Requirements should also include periodic auditing or testing.
  - » Financial assistance to offset costs for compliance should also be offered to help companies remain viable in a competitive international marketplace.
  - » Policymakers should continue to track developments in the field to identify when advances in DNA synthesis sequence fidelity, laboratory robotics, or other areas further expand the capabilities of benchtop DNA synthesis devices.

- **To support both voluntary and mandatory DNA synthesis screening practices, governments should provide guidance, resources, and/or tools to reduce ambiguity about which DNA sequences constitute a risk that should be subject to additional scrutiny and oversight.**
  - » Governments should fund the development and maintenance of publicly available biorisk databases of widely recognized biologically hazardous DNA sequences to serve as a baseline standard for sequences that should trigger additional oversight. They should also support development and dissemination of tools that perform sequence screening against government-endorsed biorisk databases. Alternatively, governments could endorse or encourage use of internationally accepted biorisk databases or screening mechanisms that meet screening criteria.
  - » Governments should work to update export control practices to make publicly available lists of genes that have been deemed export controlled on the basis of their ability to endow or enhance pathogenicity.
  - » To limit information hazards in these activities, lists and databases provided by governments should include only DNA sequences with well-established links to pathogenicity and toxicity (i.e., with information already in the public domain) and from known pathogens.

- **Governments should provide financial incentives to support adherence to DNA synthesis screening guidance and compliance with regulations.**
  - » Governments should require that all government-funded research institutions purchase benchtop DNA synthesis devices only from manufacturers that conduct customer and sequence screening.
  - » Governments should provide funding, including tax incentives or grants, for benchtop device manufacturers that conduct rigorous customer and sequence screening.

Civil society, private funders, journals, and the scientific community should provide tools and incentives for robust biosecurity practices and responsible oversight by benchtop device manufacturers. An international organization should support governance efforts by civil society and governments to ensure a coherent international oversight approach.

- **Civil society and the scientific research community should develop resources and tools to ensure that customer and sequence screening are as easy as possible for device manufacturers and that best practices are constantly improving.**
  - » These groups should develop tools to ensure that device manufacturers can easily and efficiently meet baseline standards for screening—i.e., standards set by government guidance or regulation. Such tools would support adoption of baseline standards even in countries or circumstances where screening practices are not required by governments.

  - These groups should support development of best practices among providers of benchtop DNA synthesis devices that go beyond baseline requirements. These practices could include, for example, developing strategies for customer screening, systems to prevent hacking or spoofing of sequence screening tools, and methods for reliably screening DNA of shorter lengths or using databases that capture additional risks.

- **Civil society, the scientific research community, and industry should convene discussions about the trade-offs between the desire for privacy by some benchtop synthesis device users and the risks posed by inadequate biosecurity safeguards for this technology.**

- **Private funders, such as philanthropic organizations and venture capital firms, should require that funded researchers purchase benchtop DNA synthesis devices only from manufacturers that conduct rigorous customer and sequence screening. Journals could put in place similar requirements for publication of research.**

- **Civil society, private funders, and insurers should work together to explore liability and insurance mechanisms to encourage adoption of biosecurity best practices by benchtop device manufacturers and device users.**

- **An international organization, such as the International Biosecurity and Biosafety Initiative for Science (IBBIS), should track and support civil society and government efforts to ensure a coherent international oversight approach.**

DNA synthesis technologies are fundamental to advances in bioscience and biotechnology. This new generation of benchtop DNA synthesis devices promises faster and more convenient access to DNA for researchers and technology developers, facilitating important discoveries and innovations. However, such access will also reduce barriers for bad actors, including those seeking to cause catastrophic harm. The actions recommended here will help to safeguard DNA synthesis technologies against accidental and nefarious misuse.

This field is rapidly changing, with active development, commercialization, and market expansion of benchtop DNA synthesis devices. It will be important for policymakers and others to act quickly to ensure that these technologies and companies proceed with appropriate biosecurity rules, expectations, and practices. By establishing these norms early, benchtop DNA synthesis devices can be used in a way that realizes their full benefits while minimizing biosecurity risks.

Appendix A: Participant List

Expert Interviewees

Mr. Stephen Bates
Vice President, Sales and Marketing
Molecular Assemblies

Dr. Tim Brears
Former Chief Executive Officer
Evonetix

Dr. Mike Daniels
Vice President of Product
Evonetix

Mr. James Demmitt
Senior Vice President of Operations
Biolytic Lab Performance

Dr. Thomas Demmitt
President
Biolytic Lab Performance

Dr. Dianne DiEuliis
Distinguished Research Fellow
National Defense University

Dr. James Diggans
Distinguished Scientist, Bioinformatics and Biosecurity
Twist Bioscience

Mr. Charles Fracchia
Chief Executive Officer (Former) and Founder
BioBright

Dr. Dan Gibson
Chief Technology Officer
Telesis Bio

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

Dr. Marcus Graf
Former Managing Director and Site Leader
Thermo Fisher Scientific

Dr. Gigi Gronvall
Senior Scholar, Center for Health Security
Johns Hopkins University

Dr. David Hanselman
Senior Director, Regulatory and Government Affairs
Viridos (formerly Synthetic Genomics)

Dr. Nathan Hillson
Department Head of BioDesign, Biological Systems & Engineering Division
Lawrence Berkeley National Laboratory

Dr. Jiahao Huang
Co-Founder, Director, Chief Financial Officer
Nuclera

Dr. Wesley Johnson
Microbiologist
U.S. Department of Commerce

Ms. Amanda Kobokovich
Managing Senior Analyst, Center for Health Security
Johns Hopkins University

Dr. Miao Lu
Director
Azenta Life Sciences

Dr. Jason Matheny
Chief Executive Officer
RAND Corporation

Dr. Nate Maynard
Principal Scientist, Research and Innovation
Telesis Bio

Dr. Piers Millett
Inaugural Executive Director
International Biosecurity and Biosafety Initiative for Science

Dr. Michael Montague
Senior Scholar and Research Scientist, Center for Health Security
Johns Hopkins University

Mr. Matthew Myers
Senior Mechatronics Engineering Manager
Ginkgo Bioworks

Dr. Lauren Oldfield
Director of Synthetic Genomics
Replay Therapeutics

Dr. Kimberly Orr
Microbiologist
U.S. Department of Commerce

Dr. Megan Palmer
Senior Director of Public Impact
Ginkgo Bioworks

Dr. Sean Peisert
Staff Scientist, Computing Sciences Research
Lawrence Berkeley National Laboratory

Dr. Ryan Ritterson
Executive Vice President of Research
Gryphon Scientific

Dr. Marc Salit
Director of the Joint Initiative for Metrology in Biology, Department of Bioengineering
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Ms. Blanche Savary de Beauregard
General Counsel
DNA Script

Dr. Reed Shabman
Program Officer
National Institute of Allergy and Infectious Diseases

Dr. Yue Shen
Chief Scientist of Synthetic Biology
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Dr. Andrew Snyder-Beattie
Senior Program Officer for Biosecurity and Pandemic Preparedness
Open Philanthropy

Dr. Sanjay Vashee
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Dr. Xun Xu
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BGI Group

Dr. Thomas Ybert
Chief Executive Officer and Co-Founder
DNA Script

Additional Expert Reviewers and Workshop Participants

Mr. Jens Berlips
Project Manager
SecureDNA

Dr. Kevin Esvelt
Director, Sculpting Evolution Group
MIT Media Lab

Dr. Greg McKelvey
Assistant Director of Biosecurity
U.S. Office of Science and Technology Policy

Dr. James Wagstaff
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Open Philanthropy

About the Authors

Sarah R. Carter, Ph.D.
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Dr. Sarah R. Carter is the Principal at Science Policy Consulting LLC, where she focuses on societal and policy implications of emerging biotechnologies, including issues of responsible innovation, biosafety, and biosecurity. She is currently focused on the future of the advanced biotechnologies industry, synthetic biology and DNA sequence screening, and international norms for biosecurity. In recent years, she has worked with non-profit organizations focused on these topics as well as industry, academia, and U.S. government agencies. Previously, she worked in the Policy Center of the J. Craig Venter Institute, where she led influential projects on the accelerating pace of synthetic biology and the challenges it creates for policymakers. In 2009–2010, Dr. Carter was a policy analyst at the White House Office of Science and Technology Policy (OSTP). She is also a former AAAS S&T Policy Fellow and a former Mirzayan S&T Fellow of the National Academies. She earned her Ph.D. from the University of California, San Francisco, and her bachelor's degree from Duke University.

Jaime M. Yassif, Ph.D.
Vice President, NTI Global Biological Policy and Programs

Dr. Jaime Yassif serves as NTI Vice President for Global Biological Policy and Programs, where she oversees the organization's work to reduce global catastrophic biological risks, strengthen biosecurity and pandemic preparedness, and drive progress in advancing global health security. Yassif previously served as a Program Officer at Open Philanthropy, where she led the Biosecurity and Pandemic Preparedness initiative, recommending and managing approximately $40 million in biosecurity grants, which rebuilt the field and supported work in several key areas. Prior to this, Dr. Yassif served as a Science and Technology Policy Advisor at the U.S. Department of Defense and worked on the Global Health Security Agenda at the U.S. Department of Health and Human Services. Dr. Yassif holds a Biophysics Ph.D. from University of California, Berkeley; a master's degree in Science and Security from the King's College London War Studies Department; and a bachelor's degree in Biology from Swarthmore College.

Christopher R. Isaac, M.Sc.
Program Officer, NTI Global Biological Policy and Programs

Mr. Christopher Isaac is a Program Officer for Global Biological Policy and Programs at NTI. Isaac has been involved with synthetic biology through the Internationally Genetically Engineered Machine (iGEM) Competition since the start of his scientific career and brings with him a mixture of skills in policy, biochemistry, and programming. Isaac holds a B.Sc. in Biological Sciences with a minor in Philosophy and a M.Sc. in Biochemistry (Bioinformatics) from the University of Lethbridge. He is an alumnus of the Emerging Leaders in Biosecurity Fellowship at the Johns Hopkins Center for Health Security and is a member of the iGEM Safety and Security Committee.

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Preventing the Misuse of DNA Synthesis Technology

The Common Mechanism for DNA Synthesis Screening

To safeguard DNA synthesis technologies, NTI is working in collaboration with the World Economic Forum and an international Technical Consortium of experts from across industry, academia, government, and civil society to develop an international Common Mechanism for DNA synthesis screening. This resource can help ensure that every DNA provider has access to DNA synthesis screening tools, making it easier for them to screen DNA sequences and customers efficiently and at lower cost—resulting in improved global biosecurity and biosafety.

Learn more at www.nti.org/dnasynthesis.

IBBIS International Biosecurity and Biosafety Initiative for Science

The Common Mechanism will be made available through IBBIS, which will be launched this year as an independent, international organization focused on addressing emerging biological risks posed by advances in bioscience and biotechnology.

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