Proposed Global Norms for Microbiology, Synthetic Biology, and Emerging Biotechnologies

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The aim of this paper is to develop a preliminary list of norms and best practices for life science research, to include the microbiology and synthetic biology communities. There has been extensive discussion within the NTI-led Biosecurity and Risk Reduction Initiative on how to incentivize adoption of biosecurity[1] best practices through actions taken by funders and journal editors, establishment of a seal of approval process, and standards adopted by institutions that provide key materials and services necessary for bioscience research—along with self-governance by researchers. This paper takes a deeper dive into the question: "What norms or best practices would we ideally like these stakeholders to adopt?"

The authors recognize that this has been a challenging ongoing question for the bioscience community for decades, and that we are building on many years of work in this area.[2] This paper attempts to lay out norms and best practices that are informed by the current state of life science research and biotechnology, and which can be further refined and implemented by stakeholders across the community.

In our view, the ultimate goal of developing and incentivizing widespread adoption of biosecurity norms is to deprive malicious actors of the materials, tools and knowledge necessary to produce dangerous biological agents (including those that could pose catastrophic risks on a global scale). If successful, these efforts will help ensure that the legitimate global research enterprise does not inadvertently enable malicious actors by publishing information that could be useful in designing such an agent, or by providing precursor materials necessary for production or dissemination.

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[1] Our definition of "biosecurity" for the purpose of this paper is: Measures taken to reduce the risk of deliberate misuse of biological materials, equipment or knowledge with the intention of causing harm.

[2] For example: "Recommended Policy Guidance for Potential Pandemic Pathogen Care and Oversight," <https://obamawhitehouse.archives.gov/blog/2017/01/09/recommended-policy-guidance-potential-pandemic-pathogen-care-and-oversight>; "Potential Risks and Benefits of Gain of Function Research," <https://www.nap.edu/catalog/21666/potential-risks-and-benefits-of-gain-of-function-research-summary>; "Gain of Function: Experimental Applications Relating to Potentially Pandemic Pathogens," <https://www.easac.eu/fileadmin/PDF_s/reports_statements/Gain_of_Function/EASAC_GOF_Web_complete_centred.pdf>; "Dual Use Research of Concern," <https://osp.od.nih.gov/biotechnology/dual-use-research-of-concern/>; "Synthetic Genomics: Options for Governance," <https://www.jcvi.org/synthetic-genomics-options-governance>; "Biotechnology Research in an Age of Terrorism," <https://www.nap.edu/catalog/10827/biotechnology-research-in-an-age-of-terrorism>; "Summary Statement of the Asilomar Conference on Recombinant DNA Molecules," https://authors.library.caltech.edu/11971/1/BERpnas75.pdf

As microbiology and synthetic biology capabilities become more powerful, the potential for unintended consequences and deliberate misuse are likely to increase. This paper proposes a series of norms, best practices, and actions for managing the emerging risks associated with advances in the life sciences. We start with a short list of proposed guiding principles, building on established biosecurity best practices. We then examine emerging technologies that may require additional oversight and discuss opportunities to strengthen biosecurity within the context of existing governance structures and institutions. Finally, we propose several pilot projects that could help advance these goals and discuss the key stakeholders that have a role to play in promulgating and incentivizing adherence to agreed-upon norms and best practices.

Proposed Guiding Principles for Consideration and Discussion

- Before initiating work on dangerous pathogens, closely related organisms, or other potentially harmful biological agents, a thorough risk assessment should be conducted, including an analysis of potential unintended consequences. Additional scrutiny and risk assessment are warranted under the following conditions:
    - The research involves one or more of the seven classes of experiments of concern, initially defined in 2004[3]; or
    - The research includes experiments enabled by tools and technologies developed since 2004, which may result in new classes of risk that were not previously considered. (These are discussed in greater detail in the next section.)
- A designated institutional review entity, such as an Institutional Biosafety & Biosecurity Committee, should formally review proposed research that meets either of the two above criteria. This process should include a risk assessment, which informs a decision about whether the experiments should proceed. If the benefits do not outweigh the risks, the work should not be done. If these experiments do move forward, the institutional review entity should require a risk mitigation plan.
- Proposed experiments meeting either of the two above criteria should include appropriate risk mitigation measures, including established containment, biosafety and biosecurity precautions. In some instances, such as where there is a risk of population-wide damage, multi-generational effects, or severe ecosystem disruption, specific countermeasures, antidotes, or intrinsic biocontainment (i.e., containment that is part of the microorganism itself) should be developed in parallel.
- The investigator, review committee, funder, publisher, and/or investor should consider whether there are specific types of experiments that should never be conducted. Examples for consideration could include:

[3] The seven classes of concern include experiments that would:
1. Demonstrate how to render a vaccine ineffective.
2. Confer resistance to therapeutically useful antibiotics or antiviral agents.
3. Enhance the virulence of a pathogen or render a non-pathogen virulent.
4. Increase transmissibility of a pathogen.
5. Alter the host range of a pathogen.
6. Enable the evasion of diagnostic/detection modalities.
7. Enable the weaponization of a biological agent or toxin.

From: "Biotechnology Research in an Age of Terrorism." US National Academy of Sciences. (2004).

    - Engineering a microorganism or other biological construct that is designed to cause severe, large-scale damage to human or animal life.
    - Engineering a microorganism or other biological construct that is designed to cause severe, long-term damage to the environment on a scale that would undermine its ability to support human and animal life.
    - Engineering a microorganism or other biological construct that is designed to severely impair production of agricultural staple products.
- Researchers and labs that are not working on pathogens should not use pathogen DNA. For example, researchers should refrain from using housekeeping genes (e.g., heat shock proteins, histones, or polymerases) from pathogens and should instead use DNA sequences from organisms known to be non-pathogenic. This will help maintain a clear distinction between work that requires additional oversight and scrutiny, and work that does not.
- Transparency is important in the research process to instill public confidence in the system and to open decision making to outside scrutiny and expertise. The review process for biosecurity risks and decisions on research and risk mitigation measures should be made public, though information hazards arising from the research itself should be carefully weighed.

Experiments Involving Emerging Technologies May Require Risk Assessment and More Stringent Oversight

Some research involving emerging biotechnologies, including synthetic biology tools that enable novel means of generating organisms and biological constructs, may fall into the seven categories of experiments of concern; this may create emerging risks unforeseen in 2004. These types of experiments should be subject to additional oversight, risk assessment, and in some cases, risk mitigation. Examples include:

1. Genome editing constructs targeted to human DNA sequences, combined with vectors with potential transmissibility.
2. Reconstitution of highly pathogenic viruses or closely related species, such as smallpox or horsepox.
3. Microbes or constructs that can target specific human subpopulations.
4. Microbes or constructs engineered to disrupt or damage the human microbiome.
5. Use of the synthetic biology "design, build, test" cycle to select for pathogen phenotypes associated with increased transmissibility, virulence, and ability to circumvent medical countermeasures or evade detection. The relevant technologies include advanced tools for generating large-scale libraries of bacterial and viral variants with advanced screening tools for phenotype selection.

Synthetic biology also enables the design of organisms that, while not pathogenic to human populations, present potentially significant risks for humans, animals, and the environment. These types of experiments also warrant additional oversight, risk assessment, and possibly risk mitigation. Examples include:

1. Organisms with intended or likely persistence in the environment, including those with fitness advantages over wild type (e.g., gene drives or recoded organisms resistant to phage).
2. Microbes engineered to metabolize critical infrastructure materials, such as concrete or metals, which have the potential to cause large-scale disruption.
3. Microbes or other engineered organisms with the potential to severely impair production of agricultural staples such as corn, wheat, rice, potatoes, or cassava.

We welcome feedback on this list from Initiative participants. This type of list, or a refined version of it, will likely need to be updated regularly (every 2-5 years) to ensure that new bioscience advances are captured.

Governance Structures & Institutions: Opportunities to Identify and Manage Current and Emerging Biological Risks

In addition to discussing biosecurity norms from a technology perspective, it is also useful to consider the relevant governance structures and how they can be shaped to strengthen biosecurity. Several countries have existing biosecurity guidance in place (e.g., guidance for dual use research and potential pandemic pathogens). However, these types of guidelines have not been implemented on a global scale, and they have not fully kept pace with recent technology advances. We discuss below a range of bioscience frameworks and institutions—including those focused on synthetic biology—with varying degrees of biosecurity guidelines in place, and we suggest opportunities to strengthen biosecurity elements.

Utilize Institutional Biosafety Committees (IBCs) for Biosecurity Review. IBCs are common among research institutions internationally and provide a framework for adhering to norms in the conduct of life science research. However, IBCs and the oversight they provide are focused almost exclusively on biosafety and containment. While some Committees also consider biosecurity risks, this is not universal across IBCs; it's an ad-hoc decision made by individual institutions.

Many funders, including some national governments, currently require IBC review for biosafety purposes; they could also require consideration of biosecurity issues. A prerequisite for this approach would be the development of guidance for evaluating biosecurity risks (including information hazards) and development of risk mitigation measures.

Additionally, it would be beneficial to transition these Committees from working in relative isolation. Creating a defined training program and global advisory committee that IBCs and related oversight bodies can turn to for advice would support the promulgation of global standards and help Committees achieve results that are less subjective. As an added benefit, increased coordination by these Committees could facilitate early identification of potential security concerns associated with emerging technologies.

iGEM as a Model. The iGEM (International Genetically Engineered Machines) competition is a good model for institutional biosecurity governance. iGEM subjects synthetic biology research to explicit biosecurity standards and has developed strong biosecurity norms. In fact, the iGEM competition is at the leading edge of developing biosecurity standards for synthetic biology, and it is viewed by some as a testbed for trying out new biosecurity practices and norms that can be subsequently adopted by regulatory agencies within national governments.

iGEM's biosafety and biosecurity standards, which are a requirement for participation in the competition, involve a review of projects during the research planning stage and prior to public communication about the results of the team's laboratory work. The review process enables projects with greater risk to receive additional scrutiny, such as experiments involving certain microbes, multicellular organisms, DNA sequences from pathogens, CRISPR constructs targeting human DNA sequences, prions from mammals, and some antimicrobial resistance factors. (A "white list" shows which projects do not require additional oversight.) Some types of experiments (e.g., gene drives, use of DNA sequences from listed dangerous pathogens) are prohibited in all cases. Other types of experiments (e.g., the seven experiments of concern, or those involving resistance factors for clinically important antimicrobials) are subject to in-depth review by iGEM's Safety and Security Committee. iGEM also requires that DNA sequences used by the teams undergo sequence screening for pathogen DNA.

iGEM is working to further strengthen biosecurity norms through several approaches, including: creating a dedicated award for excellence in biosafety and biosecurity, proactive outreach to iGEM teams to discuss biosafety and biosecurity issues throughout the competition cycle, and running a biosecurity session at the annual meeting that raises awareness of dual-use concerns and promotes a culture of responsibility.

Enhance DNA Synthesis Screening. The International Gene Synthesis Consortium (IGSC), which includes member companies representing approximately 80% of the global gene synthesis market, has developed a set of best practices for DNA synthesis screening. These practices were partly motivated by the U.S. Department of Health and Human Services Screening Framework Guidance[4] for DNA providers, which calls on gene synthesis companies and others to screen orders and customers to ensure that pathogen DNA[5] is only provided to legitimate researchers with a reason to have it. However, the IGSC approach has some limitations, including a lack of universal adoption globally.[6]

Funders and others could strengthen the current screening regime by requiring that researchers only order DNA from companies that conduct such screening. Such a system may

[4] https://www.phe.gov/Preparedness/legal/guidance/syndna/Pages/default.aspx

[5] i.e. DNA sequences with high homology to DNA sequences of pathogens listed on the U.S. Select Agent list or the Australia Group list

[6] This paper will limit itself to a brief discussion on DNA Synthesis Screening because it is addressed by another working group within the Initiative, as well as a separate project at the Johns Hopkins Center for Health Security.

require a third-party seal of approval or certification for companies so that researchers and research administrators know which companies meet the standard.

Add Biosecurity to Guidelines for Gene Drives and Human Genome Editing. Certain technologies and synthetic biology applications have prompted groups of funders and others to develop guidelines that address broader policy concerns. These guidelines provide a model for the seeding of principles and norms. However, to date the guidelines have been primarily focused on ethics and other challenges to societal acceptance, with no explicit language on biosecurity. These model frameworks could be expanded in scope to encompass biosecurity-focused principles:

- Gene Drive Guidelines. A consortium of funders wrote a "Principles" document[7] to ensure that Gene Drive technologies are responsibly developed. The principles include: promotion of public good and social value; stewardship, safety, and good governance; transparency and accountability; engagement with affected communities, stakeholders, and publics; and fostering opportunities to strengthen capacity and education. The funders supporting these principles (including the Gates Foundation, the Wellcome Trust, and the Foundation for the National Institutes of Health) include most, if not all, of those funding gene drive work.

- Human Genome Editing Guidelines. A variety of national and international groups have developed guidelines and nascent norms, with a focus primarily on ethical concerns. For example, the U.S. National Academies developed principles for human genome editing that include: promoting well-being, transparency (including meaningful public input), due care, responsible science, respect for persons, fairness, and transnational cooperation. The recent use of genome editing on human embryos, now babies, in China illustrates the challenge of setting norms for powerful, fast-moving technologies.

Establish Biosecurity Practices within Foundries and Companies Providing Synthetic Biology Services. Foundries and the variety of companies that provide synthetic biology tools and capabilities currently lack systematic biosecurity guidelines, and they have yet to develop screening practices analogous to those implemented by portions of the DNA synthesis industry. (This includes academic and commercial facilities that provide services for designing, constructing, testing, and/or scaling up production of microorganisms or other biological constructs—i.e. provide synthetic biology services beyond DNA synthesis). Some have expressed interest in improving in this area, but they would benefit from assistance with developing and implementing best practices.

It is important to incorporate biosecurity into foundry practices to prevent malicious actors from gaining access to materials and capabilities that could enable them to produce dangerous microbes or other biological agents, including engineered novel organisms that could cause

[7] http://science.sciencemag.org/content/358/6367/1135

damage on a global scale. We predict that the need for biosecurity within foundries will grow over time as the services they provide become more sophisticated.

Develop Laboratory Cybersecurity. Synthetic biology laboratories, including foundries, are increasingly integrated with online tools, machine learning algorithms, laboratory automation, and other cyber infrastructure. Although best practices for cybersecurity exist in other contexts, they are poorly followed in academia, particularly in life science labs. Funders could require cybersecurity best practices, where appropriate, to secure data and to reduce opportunities for tampering and misuse of laboratory equipment, for example: substituting sequence data in a pathogen database, interfering with autoclave inactivation of pathogens, or misdirection of robotic equipment handling pathogens. Such guidance could also be integrated into standards for foundries.

Taking Action to Strengthen Agreed-Upon Norms and Incentivize Adherence

Proposed Pilot Projects to Engage Researchers and Facilities

Going forward, we propose a set of pilot projects to engage researchers, technology leaders, funders, investors, publishers, insurers and other stakeholders in specific actions to manage biological risk—specifically by defining priority biosecurity norms and putting them into practice. These include:

1. Develop a biosecurity seal of approval for institutions that participate in the bioscience research enterprise as a peer-based incentive to reduce biological risk. More specifically, gatekeeper organizations—such as DNA synthesis providers, organizations that share pathogen samples, or journals that publish scientific research—could provide a seal of approval for researchers who abide by a set of agreed-upon norms and best practices, and that seal could be required for gaining access to materials or services from the organizations in question. This seal of approval concept could be explored through an initial pilot project with one to two organizations to demonstrate a proof of principle structured around the following key ideas: (1) careful risk assessment before conducting potentially dangerous dual-use research; (2) careful consideration of information hazard risks before publishing sensitive scientific research; and (3) careful risk assessment when providing potentially dual-use goods and services to a public customer base. Institutions that seek to carry out such a pilot project could make use of the proposed norms and best practices outlined in this paper as a source of ideas about the specific behaviors they would like to incentivize.

2. Convene a small international group of scientists from the virology and synthetic biology communities to develop an agreed-upon set of guidelines, which funders and institutions can use to review proposed experiments that raise security concerns (including pathogens with the potential to cause pandemics and new risks posed by emerging technologies). This project would aim to deliver a set of internationally accepted review guidelines, which have been developed and endorsed by the group of participating scientists, and which have support from numerous additional signatories.

This could be a continuation of the Cambridge Working Group[8] efforts—at least conceptually—but it would be more international and would have staffing and resource support. The guidelines produced by this project could be used by government funders, private funders, and IBCs around the world. The World Health Organization could choose to evaluate and endorse a version of these proposed guidelines to facilitate international adoption.

As a complementary piece of this effort, this group of scientists could also undertake a research project about experiments to create or modify pathogens with pandemic potential. Specifically, the research would evaluate how useful these experiments are (or are not) in vaccine development and anticipating naturally emerging infectious disease risks.[9]

3. Convene a group of foundries and companies that provide synthetic biology tools and capabilities to develop a proposed common set of protocols for screening orders and customers; the goal is to ensure that materials, tools and information with potential to cause harm are not provided to malicious actors. One or more foundries could then undertake a pilot effort to screen orders based on these protocols and test their efficacy. This would be analogous to the screening of orders and customers that is carried out in the DNA synthesis industry, but it would apply to a different set of services.

Incentivizing Adherence to Agreed-Upon Norms

As discussed above, the ultimate goal of widespread adoption of biosecurity norms is to deprive malicious actors of the materials, tools, and knowledge necessary to produce dangerous biological agents, including those that could pose catastrophic risks on a global scale. There are multiple control points that can be applied to promote norm adherence, for example:

- Funders, both public and private, can review proposed research projects to assess whether they are consistent with agreed-upon norms and make funding decisions accordingly. For awarded projects, funders can require an assessment at multiple points throughout the life of the project.
    - Governments can enforce norms and best practices through funding and regulatory mechanisms.
    - Private funders can incentivize norm adherence by including biosecurity criteria in their proposal review process.
    - Funders mandating pre-publication review can require researchers to include a section in the paper that describes the biosecurity risks posed by the research and the approaches taken to mitigate those risks.

[8] http://www.cambridgeworkinggroup.org/

[9] The authors recognize that Gryphon Scientific did important work on this topic through their 2016 report, "Risk and Benefit Analysis of Gain of Function Research." Nevertheless, additional work is warranted in our view.

- Industry and other organizations that provide tools and reagents for research effectively serve as bottlenecks for access to technologies and are therefore well positioned to promote adherence to biosecurity best practices. For example:
    - DNA synthesis companies can screen orders and customers, as discussed above.
    - Organizations and companies that provide key technologies, such as vectors and genome editing tools (e.g., Addgene[10]), can help develop and implement best practices for screening customers to ensure that only legitimate researchers have access.
    - Foundries can flesh out best practices for screening orders and customers, test and refine those practices, and then implement them more systematically.

- Publishers can require adherence to norms and best practices as a condition of publication and create new mechanisms to facilitate widespread adoption. For example:
    - Apply a "no undercut" principle, in which research rejected by one organization for risk-related reasons would not be published by a second organization without specific consultation. (This approach could also apply to funders.)
    - Add a biosecurity assessment section to the review process for all life science publications. This could include a requirement for authors to explicitly evaluate potential biosecurity risks posed by publication.

[10] Addgene is a non-profit plasmid repository. <https://www.addgene.org/>