IBBIS

International Biosecurity and Biosafety Initiative for Science

FREQUENTLY ASKED QUESTIONS

COMMON MECHANISM FOR DNA SYNTHESIS SCREENING

February 2024

The Common Mechanism is an open-source, globally available tool for DNA synthesis screening. It provides free, distributed, automated software for screening sequences of nucleic acids (including DNA and RNA) and resources to facilitate customer screening. The process for synthesis screening is shown below; the Common Mechanism provides resources to support each of these steps.

This document aims to answer some frequently-asked questions about the Common Mechanism. You may also wish to consult the following resources:

- Project webpage: https://ibbis.bio/our-work/the-common-mechanism/
- *Overcoming Challenges to Developing a Common Global Baseline for Nucleic Acid Synthesis Screening*. Wheeler et al., Applied Biosafety, 2024. Archived here.
- *Verifying Legitimacy: Findings from the Customer Screening Working Group, 2020-2023*. Tessa Alexanian, Sarah R. Carter, 2024. White Paper.

Why is screening important? What's the main goal?

Affordable commercial DNA synthesis is an essential service that supports the growing bioeconomy and is critically important for a wide range of biotechnology advances. However, synthetic DNA can be used to construct pandemic pathogens and other dangerous biological agents.

Many providers of synthetic DNA screen the orders they receive to ensure that access to dangerous DNA is only given to those with a legitimate scientific use for it and adequate risk management procedures and practices in place. DNA providers that belong to the International Gene Synthesis Consortium publicly commit to voluntarily screen synthesis orders and customers, but these companies only represent an estimated 80% of global synthesis market share. That means approximately one in five orders likely go unscreened.

At present, screening is not legally required by any national government–though some governments are beginning to explore stronger incentives for screening As the cost of DNA synthesis continues to decline over time, the fixed costs of screening orders is placing a growing financial burden on commercial providers and straining the viability of the voluntary screening model. The main goal of the Common Mechanism is to provide a tool that will give every DNA provider access to affordable synthesis screening, helping to universalize screening practices globally.

How is the Common Mechanism different from other screening tools?

The Common Mechanism is part of an emerging ecosystem of screening tools, and IBBIS shares a goal with many other providers of increasing the fraction of global orders that are screened, as well as universalizing established best practices for screening. IBBIS's contribution, the Common Mechanism, is meant to be an open, global baseline for DNA synthesis screening.

The baseline synthesis screening capabilities provided by the Common Mechanism are available for free, and the sequence screening software is designed to be installed locally by individual providers, lowering barriers to access while protecting customer data. Our biorisk screening approach, which integrates many examples to build a sequence profile for each publicly-available biorisk sequence, allows us to robustly identify sequences designed to evade screening.

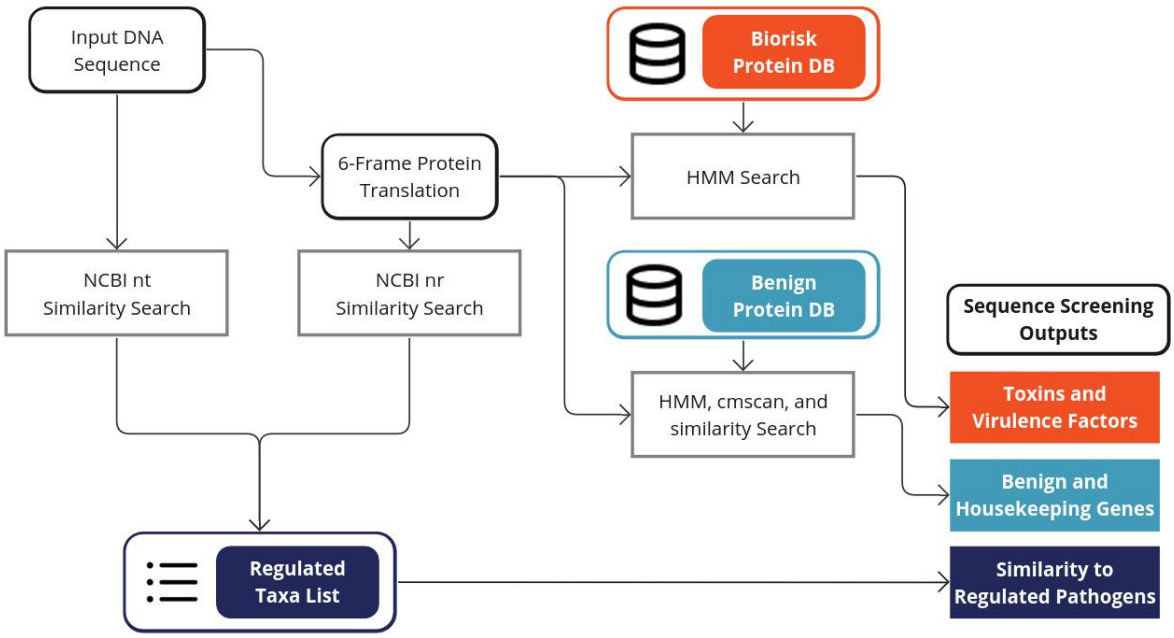
The Common Mechanism was designed with input from an international Technical Consortium, and its ongoing development will continue to involve international experts. The Common Mechanism sequence screening software will be open source, and the customer screening tools will be released under Creative Commons Licenses. IBBIS welcomes ideas for improving any of our screening tools.

How does the Common Mechanism flag sequences?

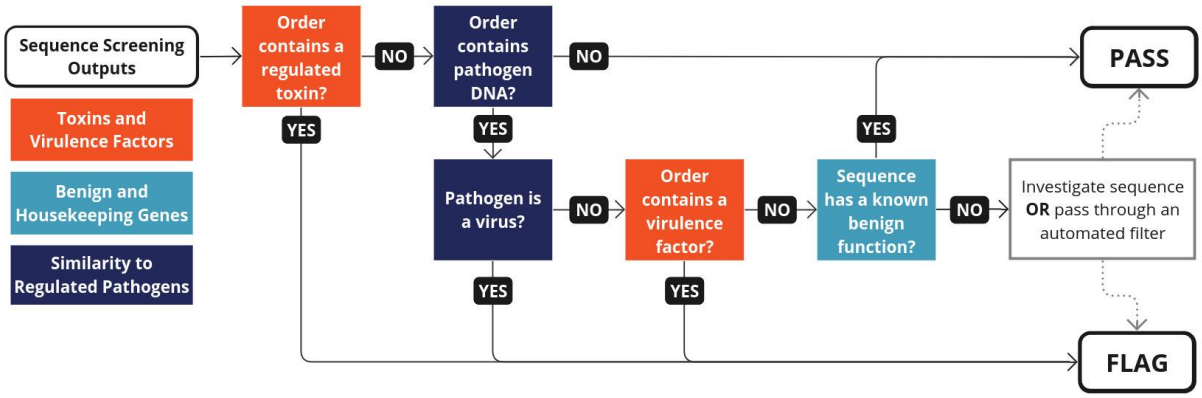
The Common Mechanism screens sequences that are 50 nucleotides or longer and flags both “sequences of concern” (i.e. virulence factors and toxins) and sequences that may be subject to export controls. The software produces three different screening outputs: flagged sequences of concern, areas of similarity to regulated pathogens, and matches to genes with a known benign function.

Sequences of concern are identified by comparing order sequences against a 'biorisk' database equipped with machine learning models capturing profiles of sequences of concern, specifically those publicly known to be associated with toxicity or pathogenicity and limited to sequences found in regulated, listed pathogens and toxins. Similarity to regulated pathogens is identified by comparing the order against publicly available DNA and protein sequences to retrieve the organism with the most closely-matching genome, then cross-referencing matches with international control lists. Benign and housekeeping genes are identified using a curated ‘benign’ database that draws from sequences found in thousands of bacterial species, RNA sequences that participate in processes essential for life, and sequences submitted to the iGEM parts registry with no associated safety flags.

This process is shown in the flowchart below.



While all screening outputs are reported, the Common Mechanism will provide an overall “pass” or “flag” decision for an order according to the flowchart below.



The Common Mechanism will allow all nucleic acid synthesis companies to adopt baseline screening practices at no cost beyond computing, and to maintain screening in-house, without the need to send their customers' sequences outside of the company.

What do I need to install the Common Mechanism?

Installing the Common Mechanism sequence screening software requires a computing environment which can run shell scripts and Python (it has been tested in Linux computing environments) with adequate storage space for the databases used (~1 Gb for the curated biorisk and benign databases, ~600 Gb for the standard protein and nucleotide databases used for similarity search, which will already be installed in many bioinformatics computing environments). The first production release of the sequence screening software will support running only the biorisk and benign parts of the screening pipeline, and we also expect to make available an API for testing small numbers of sequences.

Can I get access to the Common Mechanism?

Yes! The Common Mechanism is currently in an open beta, and interested users of the software should contact us to test it. You can also inspect the code and databases (currently in a beta version, and expected to change in response to test feedback) online if you wish. A production release of the sequence screening software is expected in early Q2 2024.

How does the Common Mechanism address the needs of benchtop devices?

The Common Mechanism sequence screening was developed with a dual emphasis on reducing ambiguities and flagging a baseline level of sequences of concern, making it a useful tool for benchtop synthesis devices. The decision support tool is able to provide

a fully-automated “flag” or “pass” decision for each order; benchtop devices could then be configured to refuse to synthesize sequences that are flagged during screening. Legitimate users of those sequences would need to order them from another commercial provider or provide an authentication key that allows them to synthesize specific sequences of concern.

Does the Common Mechanism expose my orders?

No. The Common Mechanism is designed to be locally installed by synthesis providers, keeping all customer information in-house.

How does the Common Mechanism manage security of the biorisk database?

The initial “biorisk” database used by the Common Mechanism draws only from existing, publicly available databases of sequences known to be associated with toxicity or pathogenicity. This list is further limited to only those sequences that are found in regulated, listed pathogens and toxins, such as those on export control lists. This limited biorisk database allows the Common Mechanism to flag sequences that are well established, transparently sourced, and represent some level of international consensus. As such, sharing the initial databases does not present a security concern.

Who developed the Common Mechanism?

The Common Mechanism was initially proposed in 2020 by an international working group jointly convened by the Nuclear Threat Initiative (NTI) and the World Economic Forum (WEF), which also called for an international entity that will house the mechanism, promote its adoption, and work to establish global norms for nucleic acid synthesis screening. Later that year, NTI and WEF launched the Technical Consortium to inform the design of the Common Mechanism, consisting of African, Asian, European and North American experts from industry, academia, philanthropy, and international organizations. From 2020–2023, this Consortium guided the design of the baseline Common Mechanism screening process, and its ongoing development will continue to involve international experts.

The Common Mechanism software and databases were developed by a team of technical consultants working with NTI, led by Dr. Nicole Wheeler of the University of Birmingham, and including contributions from Brittany Rife Magalis of the University of Louisville and Jennifer Lu of the Center for Computational Biology at Johns Hopkins University.

In 2024, IBBIS was launched to act as a long-term home for the Technical Consortium and Common Mechanism, as well as to support related initiatives in advancing biosecurity.

Who funds the Common Mechanism?

The Common Mechanism has its long-term home within IBBIS, a Switzerland-based independent international organization that has received funding from philanthropic organizations based in Europe and North America.

What if I need help using it? How should I contact IBBIS?

For general inquiries, please get in touch with IBBIS at info@ibbis.bio. Our technical staff and consultants are available to support beta testers of the sequence screening software, and will guide you through the installation process; please contact us if you are interested in testing it.