ThreatSEQ™ Web Service: Advanced DNA Screening Platform

**Helping the synthetic biology community perform research responsibly:**

- Battelle's ThreatSEQ™ web-based analytical software tool and service provides a powerful new approach to reduce the potential for unintended production of DNA sequences of concern.

- Built on more than a decade of research, our tool quickly and accurately detects DNA sequences of concern and provides this information to the user in a concise report.

- This analysis enables biotechnology companies to make faster, more informed decisions to protect themselves, their clients and society from potential biosecurity risks.

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HIGH-SECURITY SYSTEM ARCHITECTURE

Battelle's ThreatSEQ web service has been designed to protect the confidentiality and integrity of client data and has been implemented in accordance with the ISO/IEC 27000 series of standards for cybersecurity and information security. The system utilizes a cloud-based architecture hosted on Amazon Web Services (AWS). The Amazon GovCloud offering was chosen to ensure compliance with the most stringent security standards and to provide the flexibility to support a wide variety of clients.
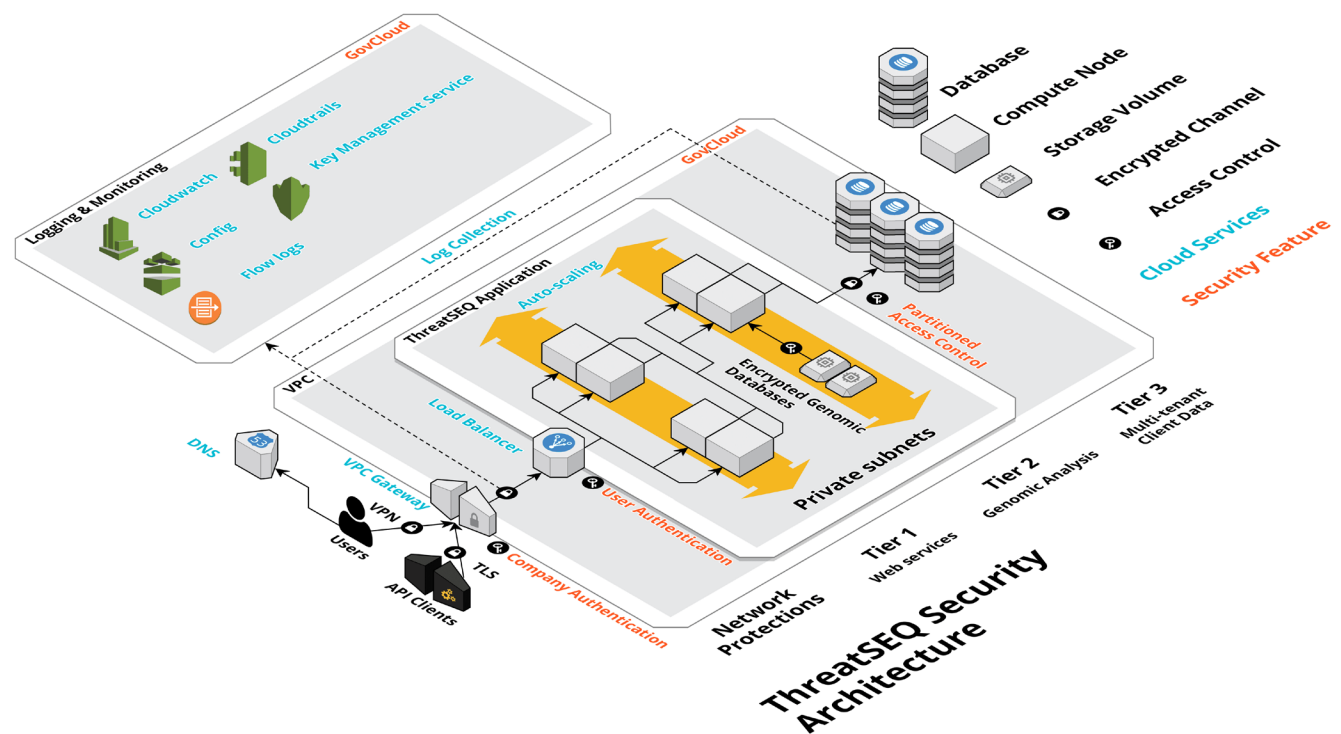
Client Data Handling

Client data is stored within secure AWS-managed databases and is encrypted using service unique keys. Client data is partitioned using individualized access controls to prevent client data exposure. Multiple event and behavior monitors are in place to ensure only authorized access to client data occurs, and all access is logged to provide a record of data access.

Access Protections

A two-stage process is used to restrict access to the web service. The first stage limits access to known client organizations, and the second stage individually identifies users or service connections.

Network and Communication Protections

All internal and external communications are encrypted using the robust cryptographic services provided by AWS GovCloud, which are validated against the United States National Institute of Standards and Technology (NIST) Federal Information Processing Standard (FIPS) 140-2. Individual client user access is protected using encrypted communications, and automated access to the service interface is protected by an encrypted Virtual Private Network (VPN) connection.

HOW IT WORKS

The ThreatSEQ web service detects and classifies sequences of concern in genomic data. The foundation of the platform is four databases, including a proprietary highly curated sequence of concern database. These databases are coupled to an aligner, and all alignment results are processed for hits to databases consistent with current Department of Health and Human Sevices (HHS) guidelines.[1] The hit profiles across the databases are subsequently processed for a threat ranking that is displayed to the end user through a graphical user interface.

Sequence of Concern Database

The gene-level database was built on more than a decade of research into the factors that make pathogens dangerous. It compiles more than 10,000 sequences of concern comprising 850 sequence types of concern from 75 species of bacteria, 96 viruses, 12 eukaryotic pathogens and other contributors to pathogenesis.
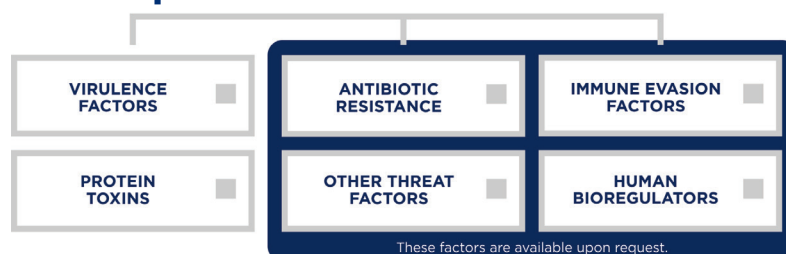
The database covers 100% of human U.S. Select Agents and Australia Group Lists (Tier 1) and virtually all known bacterial human/zoonotic pathogens.[2, 3] To ensure that the most comprehensive comparison is performed, the user also is provided with results against the full genomes of organisms derived from the National Center for Biotechnology Information (NCBI) database and from select agent registries around the world.

Threat Identification Algorithm

The algorithm rapidly scans a requested DNA sequence and looks for matches within the databases. Matches may be entire gene sequences or parts of gene sequences. Our tool has been designed to operate efficiently and to detect complex patterns (e.g., tiled mosaic DNA fragments).

In addition to identifying positive matches, the ThreatSEQ algorithm provides information about the types of threats that a gene sequence may present by providing information about the structures of the genes and their resulting functions. The existing analysis is supported by more than 4,400 peer-reviewed papers, and Battelle continues to update the database and algorithm as new research emerges.

Sequence of Concern Database

| VIRULENCE FACTORS | ANTIBIOTIC RESISTANCE | IMMUNE EVASION FACTORS |
| PROTEIN TOXINS | OTHER THREAT FACTORS | HUMAN BIOREGULATORS |

These factors are available upon request.

ThreatSEQ Rapid DNA Analysis for Sequences of Concern

DNA Order
GTAC TGCC AGGT

Gene Synthesis Company
GTAC TGCC AGGT

Battelle
GTACTGCC

Gene Synthesis Company

[1]https://www.phe.gov/Preparedness/legal/guidance/syndna/Documents/syndna-guidance.pdf.
[2]Federal Select Agent Program 2017. Select agents and toxins list. www.selectagents.gov/SelectAgentsandToxinsList.html. Division of Select Agents and Toxins, Centers for Disease Control and Prevention, Atlanta, GA.
[3]The Australia Group 2017. Australia Group common control lists. www.australiagroup.net/en/controllists.html.

THREAT REPORTING

The ThreatSEQ web service provides an easy-to-understand report that flags each identified sequence of concern and characterizes the potential hazard associated with the sequence. The report provides the reviewer with actionable information to easily determine the threat level of a sequence and to understand the rationale behind the threat determination.

Threats are ranked for more efficient review:

TIER 1 = matches a known sequence of concern or Tier 1 virus

**TIER 2 =** matches any sequence in a non-annotated select agent's genome

TIER 3 = matches a non-concerning sequence in an annotated select agent's genome

TIER 4 = at least one 200bp segment had a best match alignment to a select agent's genome

NON-THREAT = matches a sequence in a non-select agent's genome

**UNIDENTIFIED =** Sequence could not be found in any database

BELOW DETECTION LIMIT = Sequence is less than 200bp
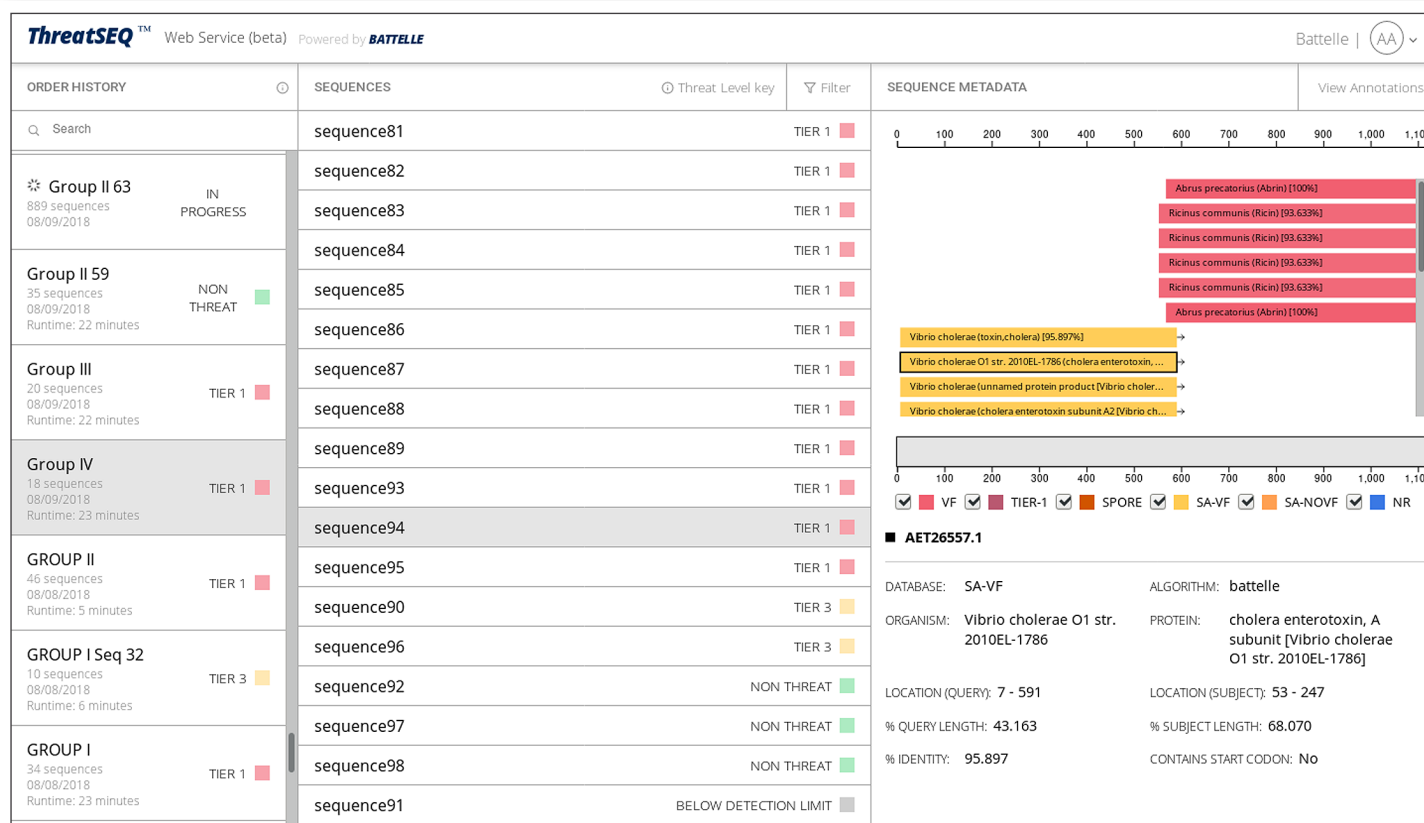
Reviewers can run reports of order history and threat status for easy tracking and auditing of screening results.

FEATURE OVERVIEW

The ThreatSEQ web service threat assessment algorithms have been designed to detect sequences of concern that are in either chimeric or mosaic form. The platform provides the end user with an advanced graphical user interface to review the results for the submitted sequences, which includes high-quality metadata and a context mapping tool that allows the user to see how alignments pair to the query sequence.
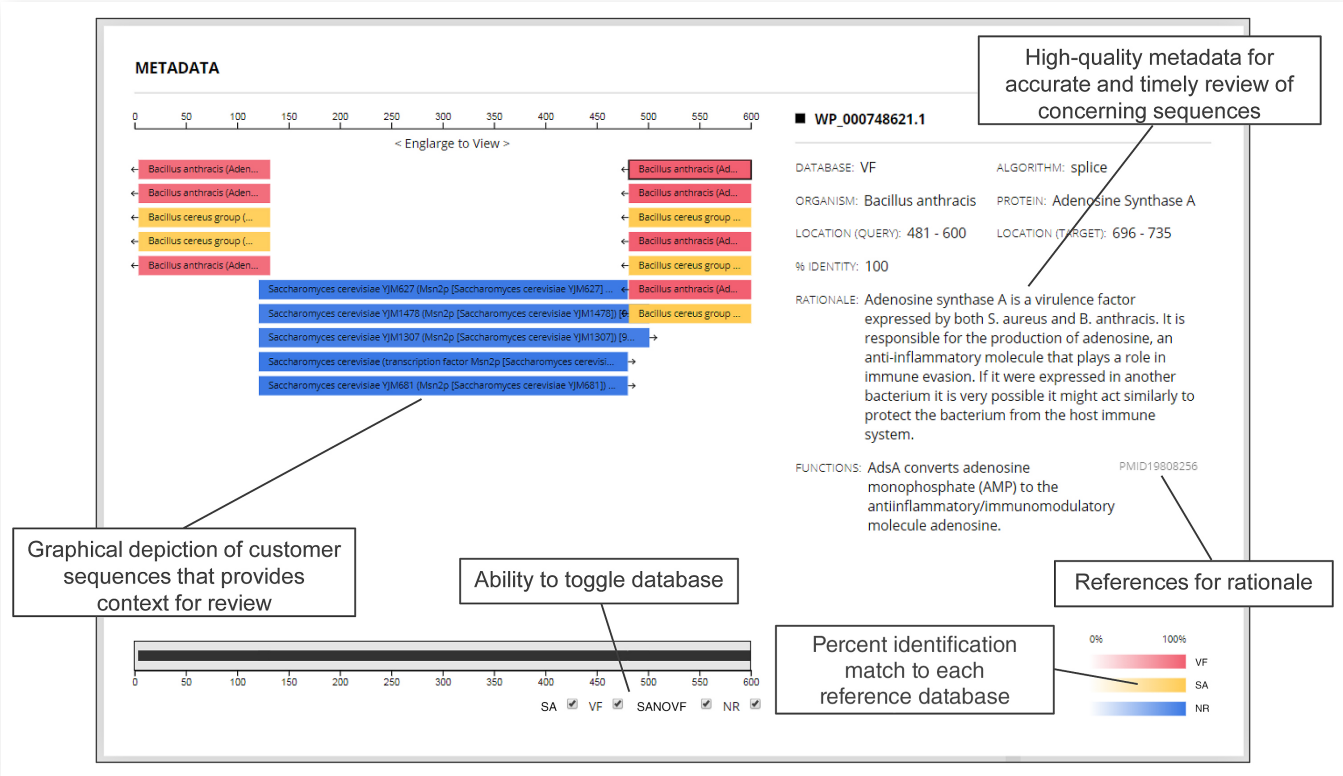
FEATURES	BATTELLE	Current Practice
■ High-Security	✓	✓
■ Company-Specific	✓	✓
■ Virulence Factor Focused	✓	--
■ Linked Metadata	✓	--
■ Continuous Updating	✓	--
■ Standardized and Objective Threat Status Score	✓	--
■ Complex Pattern Identification	✓	--
■ Comprehensive Reporting and Interpretation	✓	--
■ High Accuracy	✓	--
■ Web-Deployed	✓	--
■ Focused Input	✓	--

Battelle's ThreatSEQ web service delivers:

Periodically updated database: established pipeline for routine database updates

Efficiency: highly curated database and custom algorithms reduce false positives compared to current screening methods

Accessibility: secure cloud-deployed solution with automated sequence-specific threat detection significantly reduces required infrastructure and subject matter expert (SME) labor

Reduces customer follow-up time: consolidated reporting and links to original data sources and rationale

Who is Battelle?

We are the world's largest independent, nonprofit research and development organization, operating at the forefront of scientific discovery. We apply cutting-edge methods to some of today's most complex biosecurity challenges. At Battelle, you'll find:

- **Expertise:** We bring together leading experts in applied genomics, immunology, toxicology, bioinformatics, chemical and biological warfare defense, advanced analytics, cybersecurity and a host of related disciplines to develop multidisciplinary approaches to solve biosecurity problems.

- **Experience:** We have spent more than a decade building our proprietary database of virulence factors and other sequences of concern. We bring a deep understanding of the factors that make genetic sequences potential biosecurity threats.

- **Objectivity:** Our research is grounded in solid, objective science and proven methods. We continually reinvest in original research that benefits our clients and society.

Ready for a new approach to biosecurity risk reduction? Contact us for a demo.

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It can be done