RADx-rad: Comparative Analysis of Novel Diagnostic Methods for SARS-CoV-2 Detection and Surveillance

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Comparative Analysis of Novel Diagnostic Methods for SARS-CoV-2 Detection and Surveillance

The RADx℠ Radical program (RADx-rad) is advancing non-traditional diagnostics to improve SARS-CoV-2 detection, surveillance, and response. This study compares novel diagnostic methods for detecting SARS-CoV-2 and its variants, including electronic noses (VOCs in breath), chemosensory testing (at-home olfactory assessment), and automatic detection technologies (microfluidic saliva assays for viral and antibody detection). It also evaluates technologies, such as electrochemical sensors, touch-based detection, mechanical detection, and aerosolized virus monitoring, alongside biosensing platforms like smart masks.

Methods are assessed based on analyte targets (spike protein, protease, antibodies), specimen types (saliva, blood, breath), and biophysical techniques. Key performance metrics include sensitivity, specificity, area under the curve (AUC), and limit of detection (LoD), with validation across diverse populations and SARS-CoV-2 variants. Cross-reactivity with common respiratory viruses such as influenza and human coronaviruses is also examined to ensure diagnostic specificity.

This comparative analysis will guide the selection of optimal diagnostics for point-of-care and at-home-testing, improving pandemic response and preparedness for COVID-19 and future infectious diseases. The innovative and complementary diagnostic methods developed by the RADx-rad program offer practical solutions for rapid deployment and scalable impact in real-world infectious disease surveillance.

RADx-rad Research Areas

RADx-rad research areas are diverse and can be grouped into three major research areas:

- Wastewater-based surveillance (7)
- Diagnosis of multisystem inflammatory syndrome in children (MIS-C) (8)
- **Novel diagnostic method development (35)**

Study Objectives

- Evaluate the use the NIH RADx Data Hub to access and analyze RADx-rad dataset
- Review the data elements used to describe RADx-rad datasets
- Characterize the diagnostics methods developed by RADx-rad
  - Technology metadata
  - Samples and specimens used for validation
  - Performance metrics
- Demonstrate the diversity of diagnostic methods

Motivation: Traditional Testing Methods have Limitations

- **PCR (Polymerase Chain Reaction)**

  ✅ High sensitivity, detects asymptomatic cases

  ❌ Long turnaround time (24-48 h), lab required, labor-intensive, expensive

  🩺 *Use*: Confirm active infection

- **Antigen (Rapid) Test**

  ✅ Fast (15-30 min), easy access, inexpensive

  ❌ Less accurate, false negatives possible

  🩺 *Use*: Quick screening

- **Antibody Test**

  ✅ Shows past infection, research tool

  ❌ Not for current diagnosis

  🩺 Population studies

Novel Diagnostic Method Development 1

Research Topics

- **Electronic Noses:** Developing portable breath analysis and electronic nose technology for COVID-19 detection through volatile organic compounds (VOCs)
- **Chemosensory Testing:** Implementing rapid, self-administered, and at-home chemosensory tests to detect and assess olfactory function and chemosensory loss in COVID-19 patients
- **Exosome-based Technologies:** Utilizing saliva-based and microfluidic technologies to detect SARS-CoV-2, antibodies, and respiratory pathogens, and to predict outcomes in COVID-19 patients through the analysis of exosomes

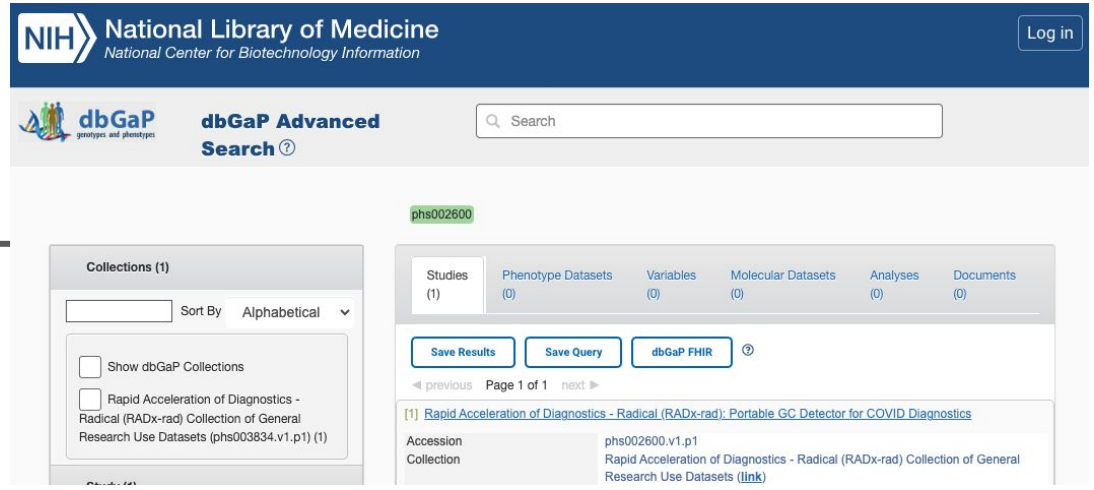
Novel Diagnostic Method Development 2

Research Topics

- **Novel Biosensing:** Developing novel technologies, including home-based diagnostics, and breathalyzers for rapid and sensitive detection of SARS-CoV-2
- **Automatic Detection and Tracing:** Developing technologies for SARS-CoV-2, including privacy-protected contact tracing, electrochemical sensors, touch-based detection, mechanical detection, and aerosolized virus detection
- **Multimodal Surveillance:** Utilizing multimodal data sources and smart technologies for early detection and surveillance of COVID-19 in various populations, including dialysis facilities and through smart masks

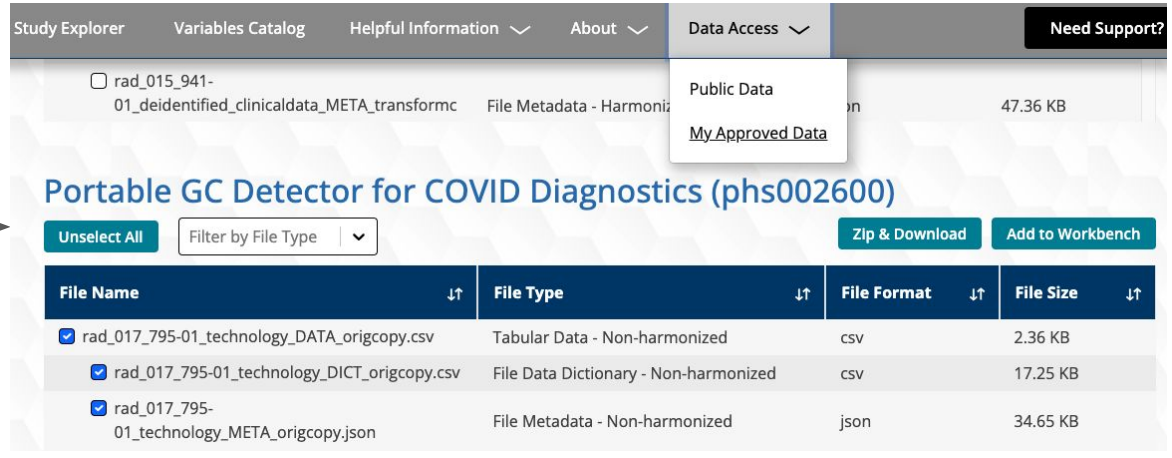
RADx® Data Hub | How to Access RADx Datasets

1. Select studies in dbGaP or RADx Data Hub

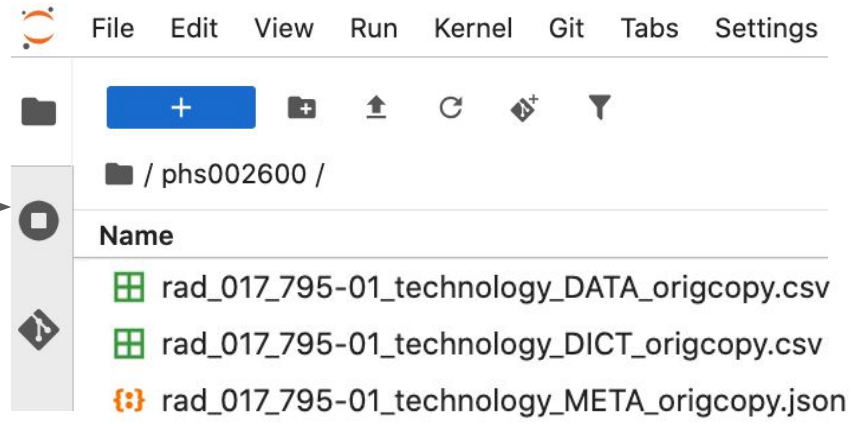


2. Apply for data access in dbGaP

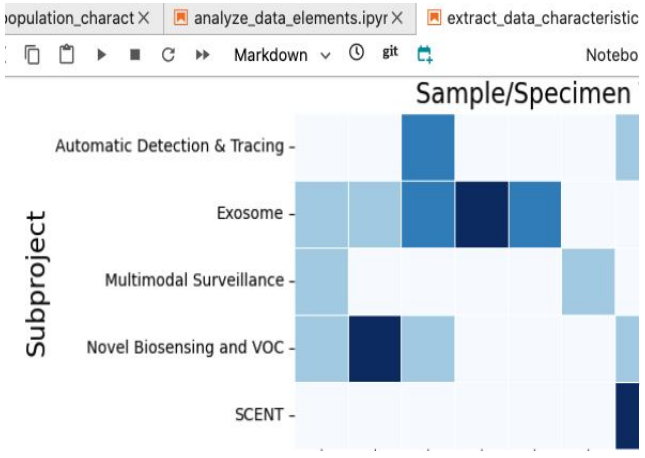
3. Select approved datasets & add to Workbench



4. Access datasets in Jupyter Lab



5. Perform Analysis



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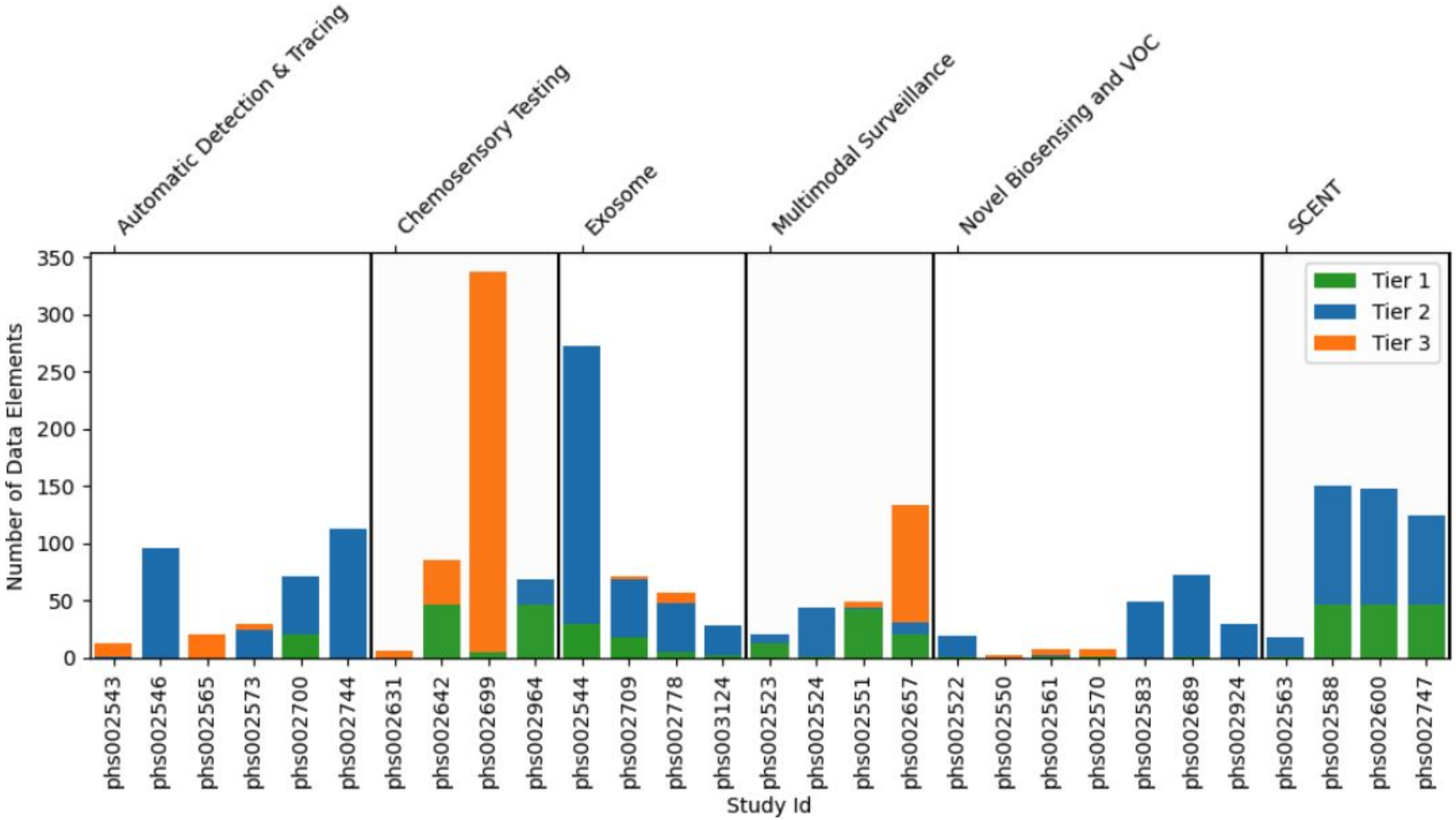
Dataset Selection

- Added all RADx-rad datasets to the workspace
- Used the META data files to select the six technology development project-related studies
  - SCENT
  - Chemosensory Testing
  - Exosome
  - Novel Biosensing and VOC
  - Automated Detection & Tracing
  - Multimodal Surveillance

Data Element Harmonization Status



Data Element Tiers

Tier 1: RADx harmonized demographic and medical history data elements

Tier 2: RADx-rad-specific harmonized data elements (used in this study)

Tier 3: RADx-rad study-specific data elements

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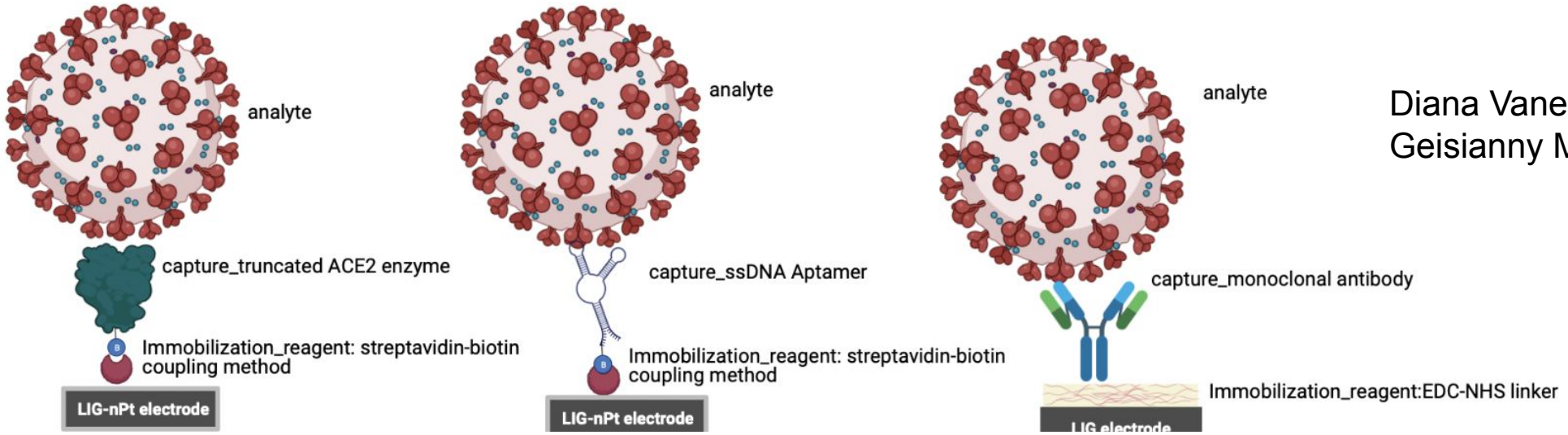
Tier 2 Data Element Development



Diana Vanegas,
Geisianny Moreira

capture_*receptor*_source capture_*receptor*_source_name capture_*receptor*_target_organism …	capture_*aptamer*_source capture_*aptamer*_source_name capture_*aptamer*_target_organism_ …	capture_*antibody*_source capture_*antibody*_source_name capture_*antibody*_target_organism …	generalization
capture_receptor_region capture_receptor_region_start capture_receptor_region_end …	capture_aptamer_sequence capture_aptamer_Kd …	capture_antibody_host_organism capture_antibody_clonality …	specialization

Comparative Analysis of Novel Diagnostics Methods

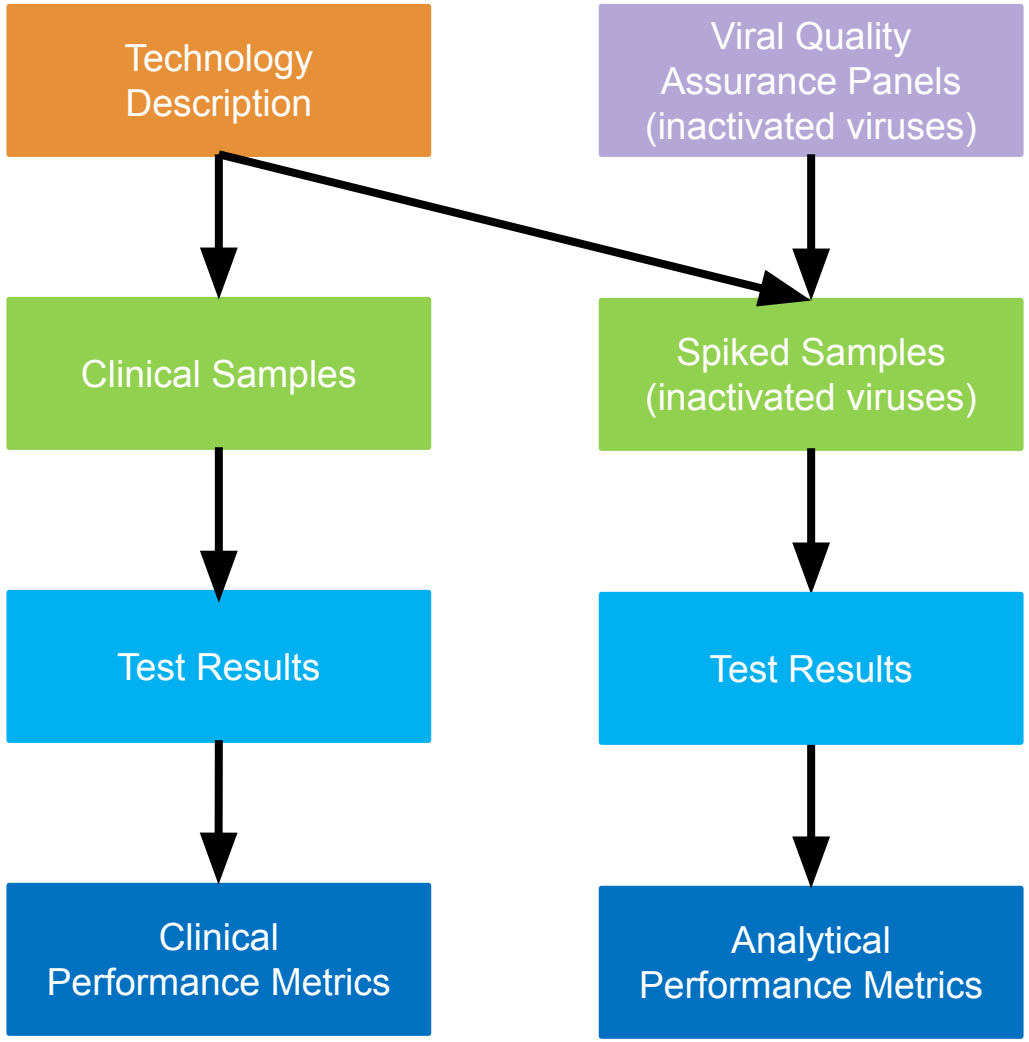
Method Characteristics

- **Analyte**: Spike protein, protease, antibodies
- **Biophysical Techniques**: SARS-CoV-2/COVID-19 detection methods
- **Specimens Used**: Saliva, breath, odor

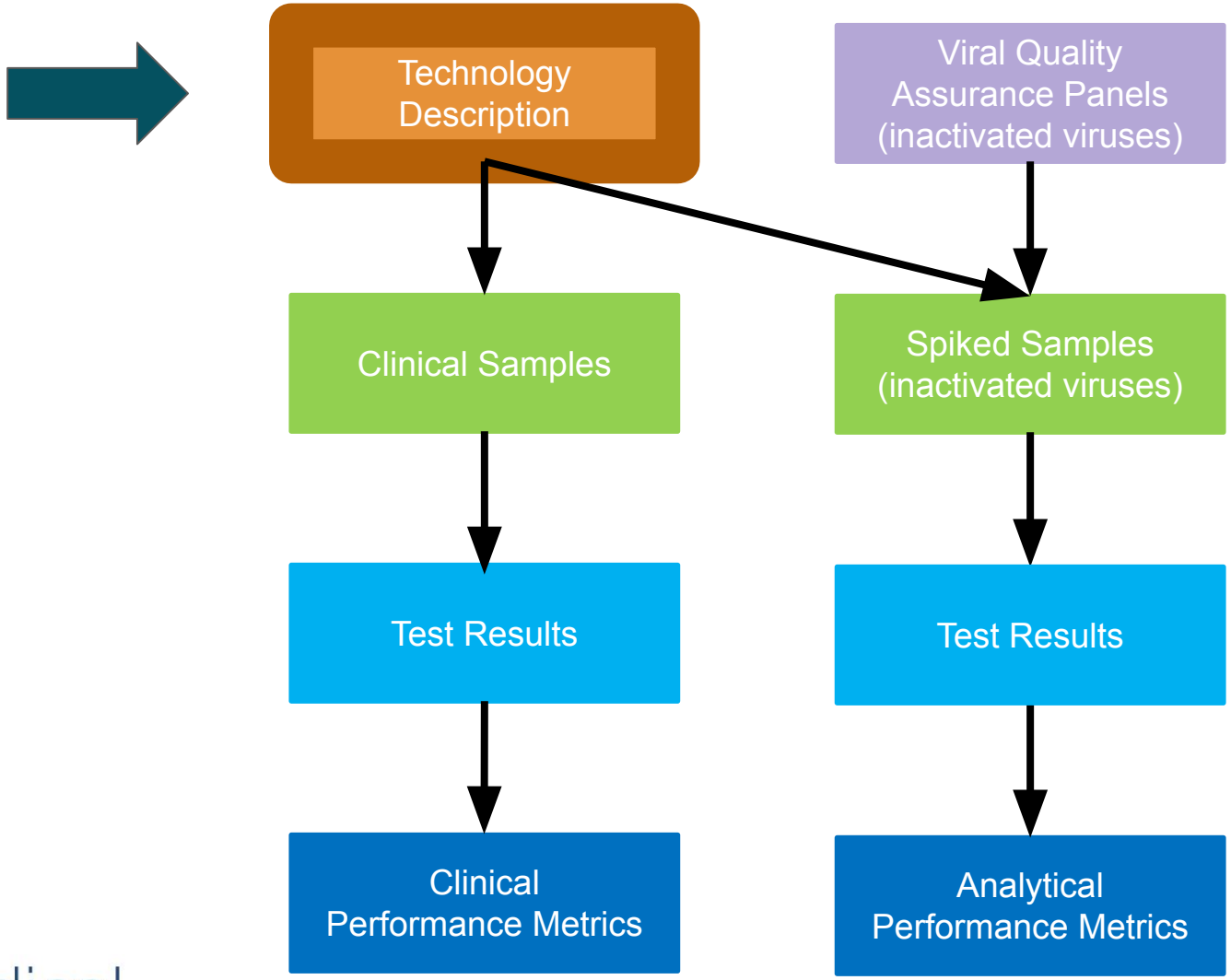
Method Validation

- **Variants Tested**: SARS-CoV-2 variants
- **Cross-Reactivity**: Influenza, HCoVs
- **Clinical Testing**: Study demographics
- **Performance Metrics**: Sensitivity, specificity, AUC, limit of detection

Data Organization for Diagnostic Method Development Projects



Technology Description - Metadata



Technology Description

Aptamer-Antibody Sandwich ELISA

technology_platform: sandwich ELISA

substrate

technology_description: sandwich enzyme-linked immunosorbent assay

biorecognition elements:

signal_detection: chemiluminescent

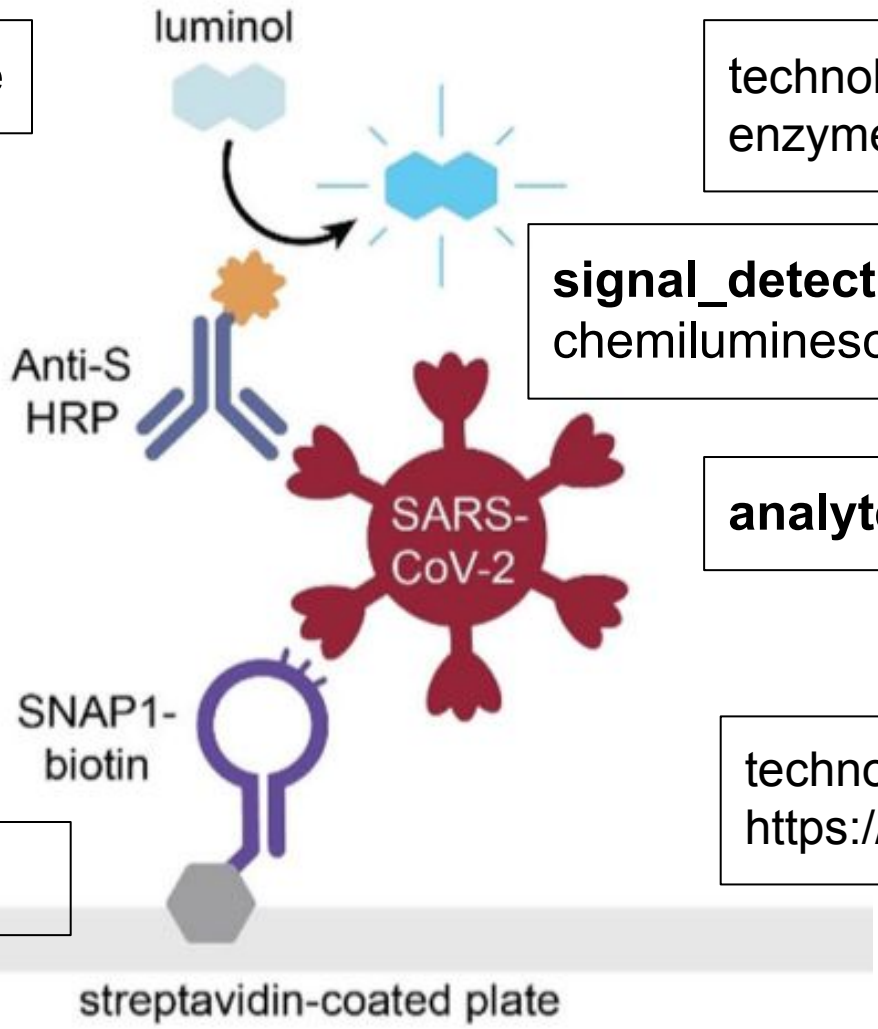
detector_antibody

analyte_type: virus

capture_aptamer

technology_reference: https://doi.org/10.1002/anie.202107730

surface: streptavidin-coated plate



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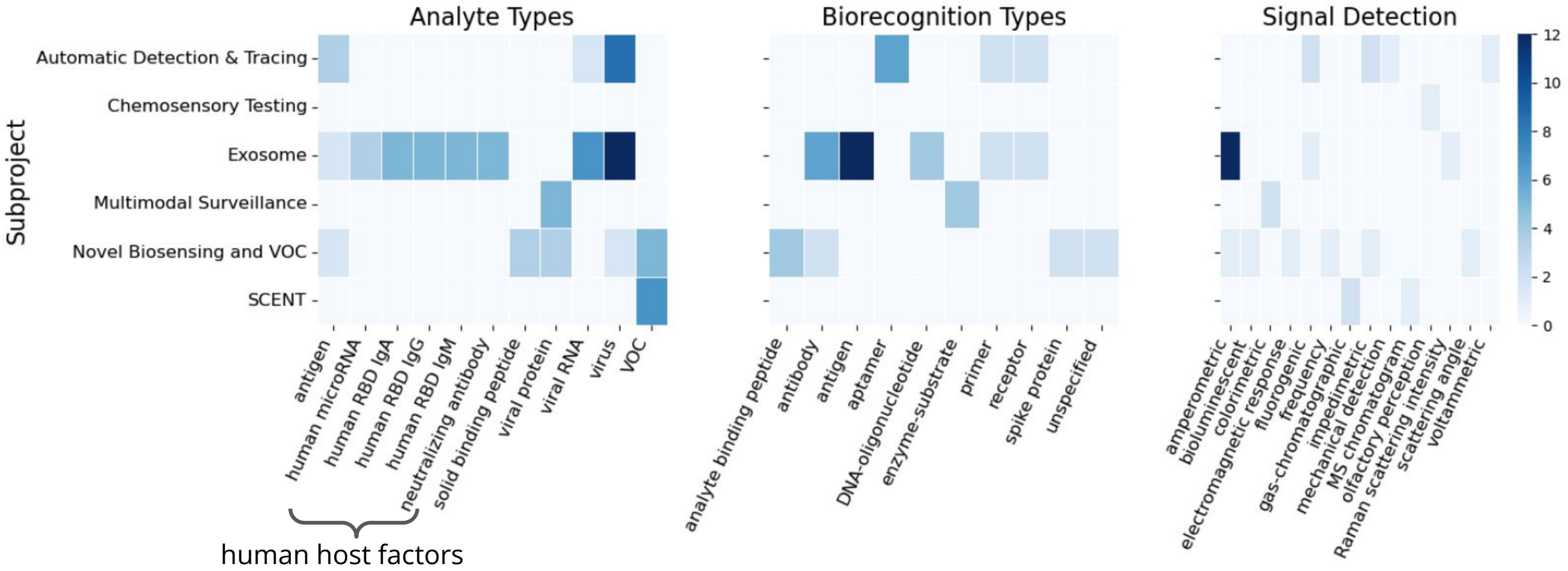
Diverse, Complementary Approaches to COVID-19 Diagnostics

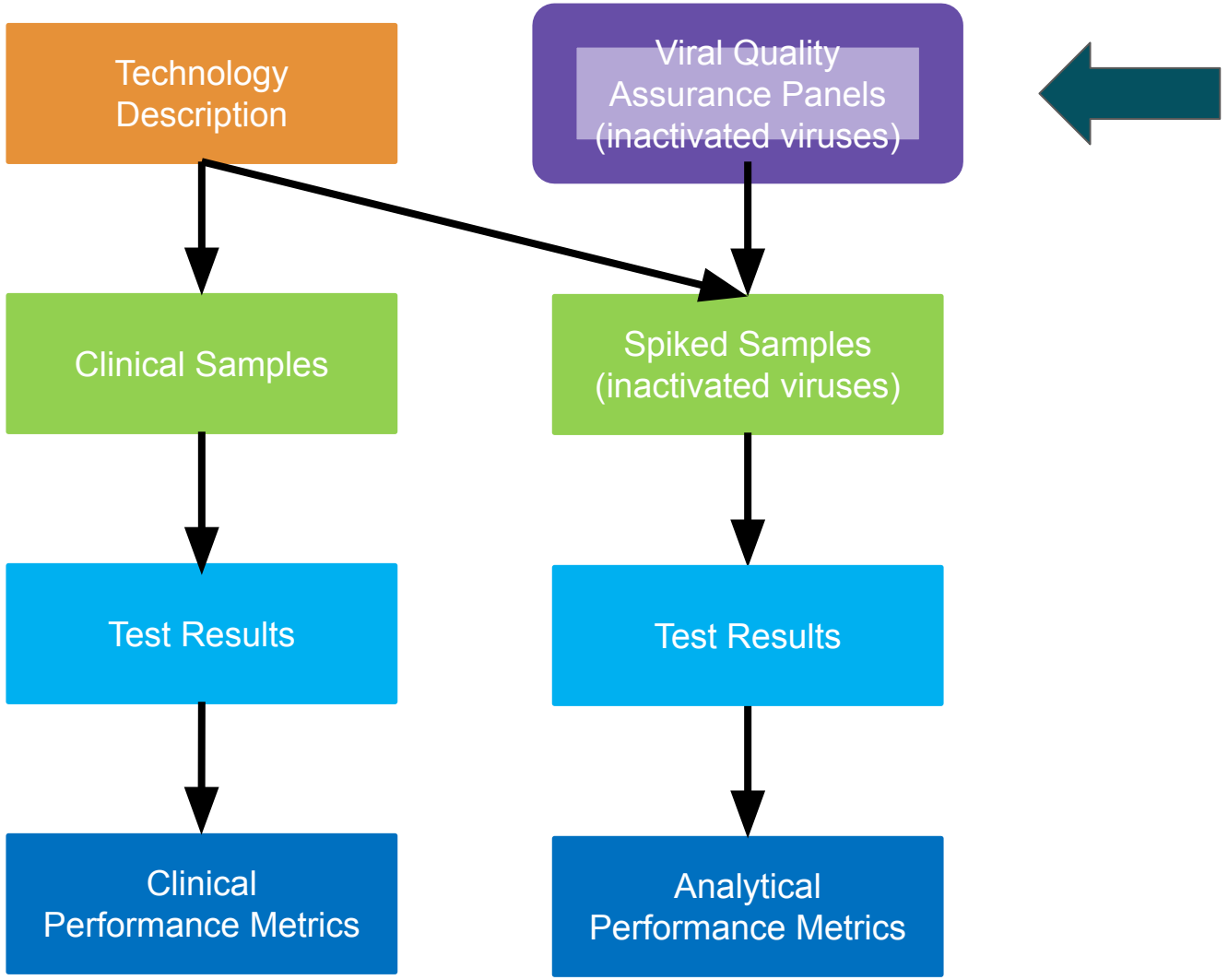


The specific target substance that a diagnostic method detects to indicate the presence of SARS-CoV-2 or COVID-19

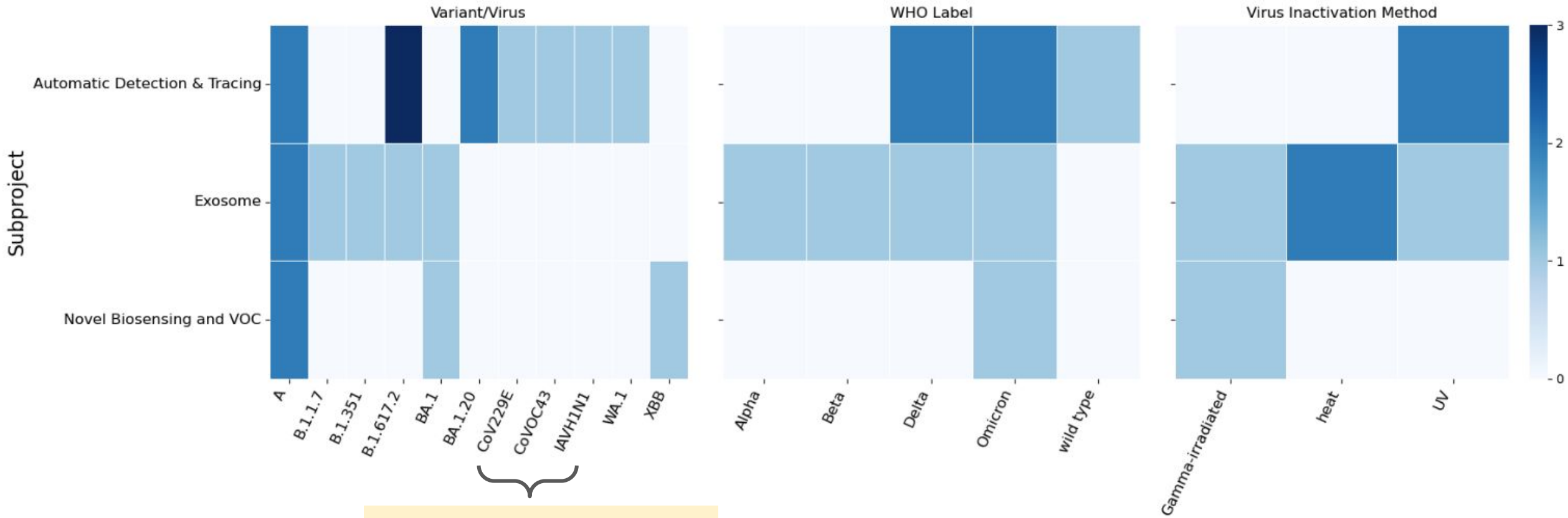
The molecular mechanism or component used to specifically bind to the analyte.

The physical or chemical technique used to quantify the recognition event between analyte and biorecognition element.

Viral Quality Assurance Panel



Diverse Variants for Method Validation - Inactivated Viruses



Evaluated cross-reactivity against common respiratory viruses (human coronaviruses, influenza)

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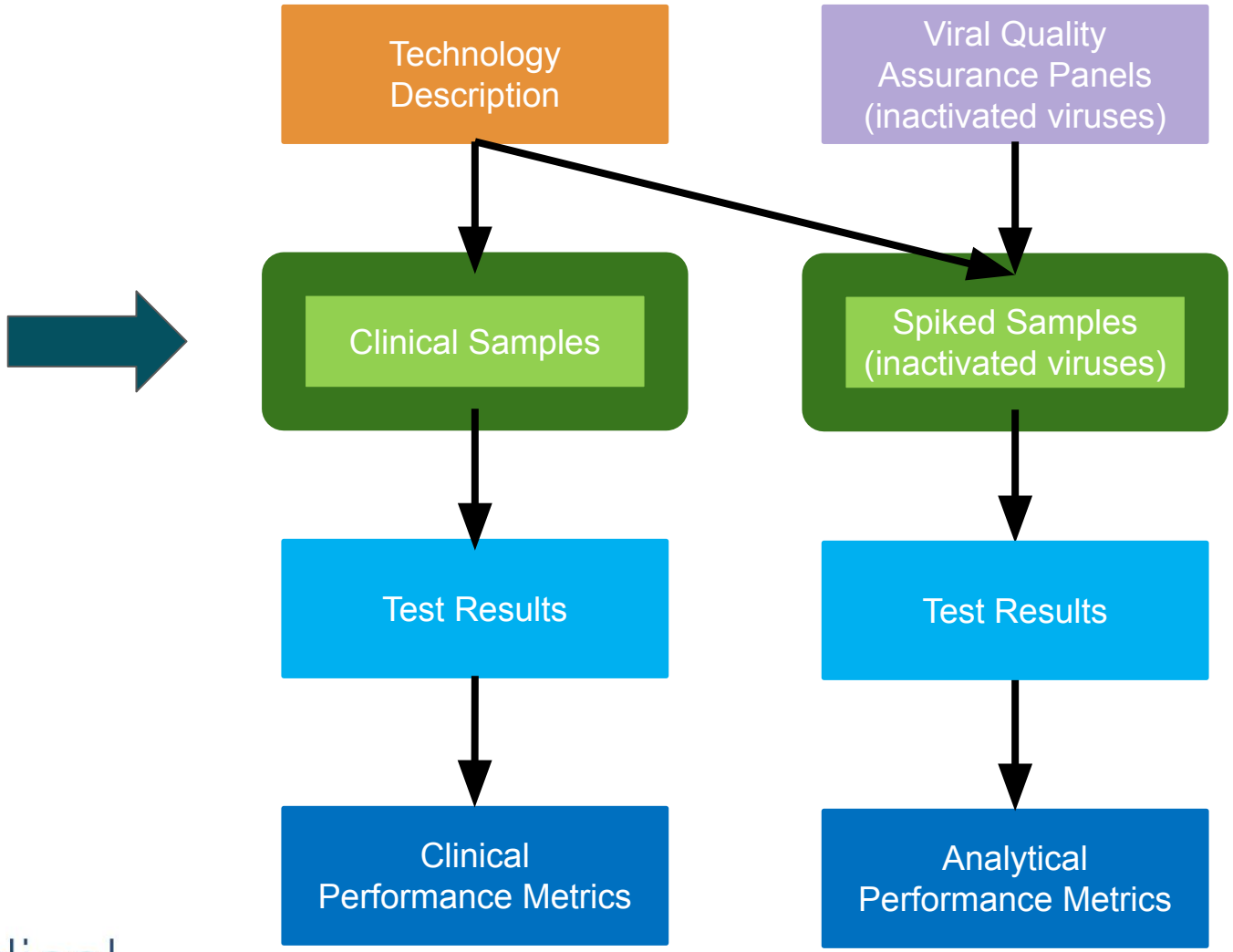
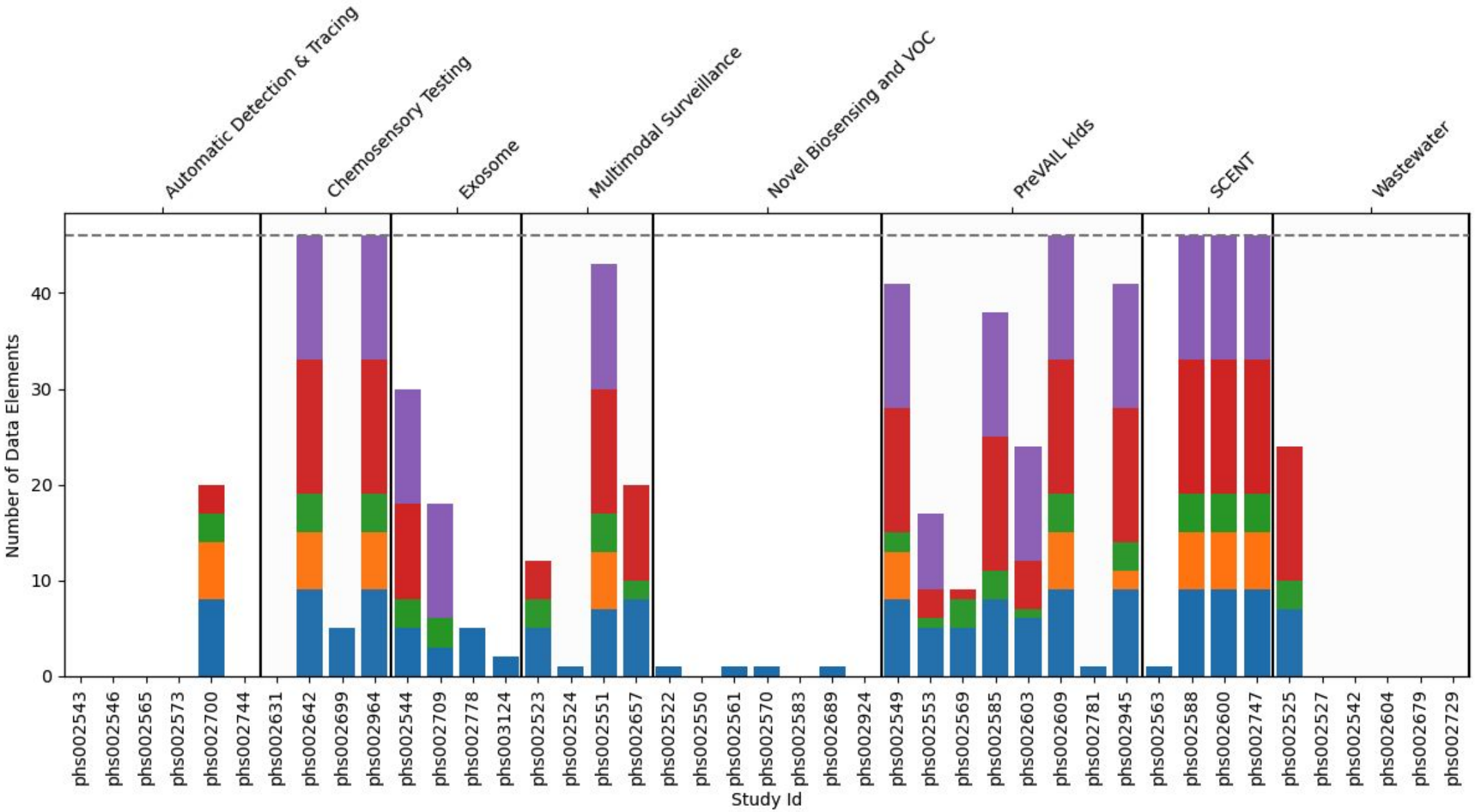
Samples

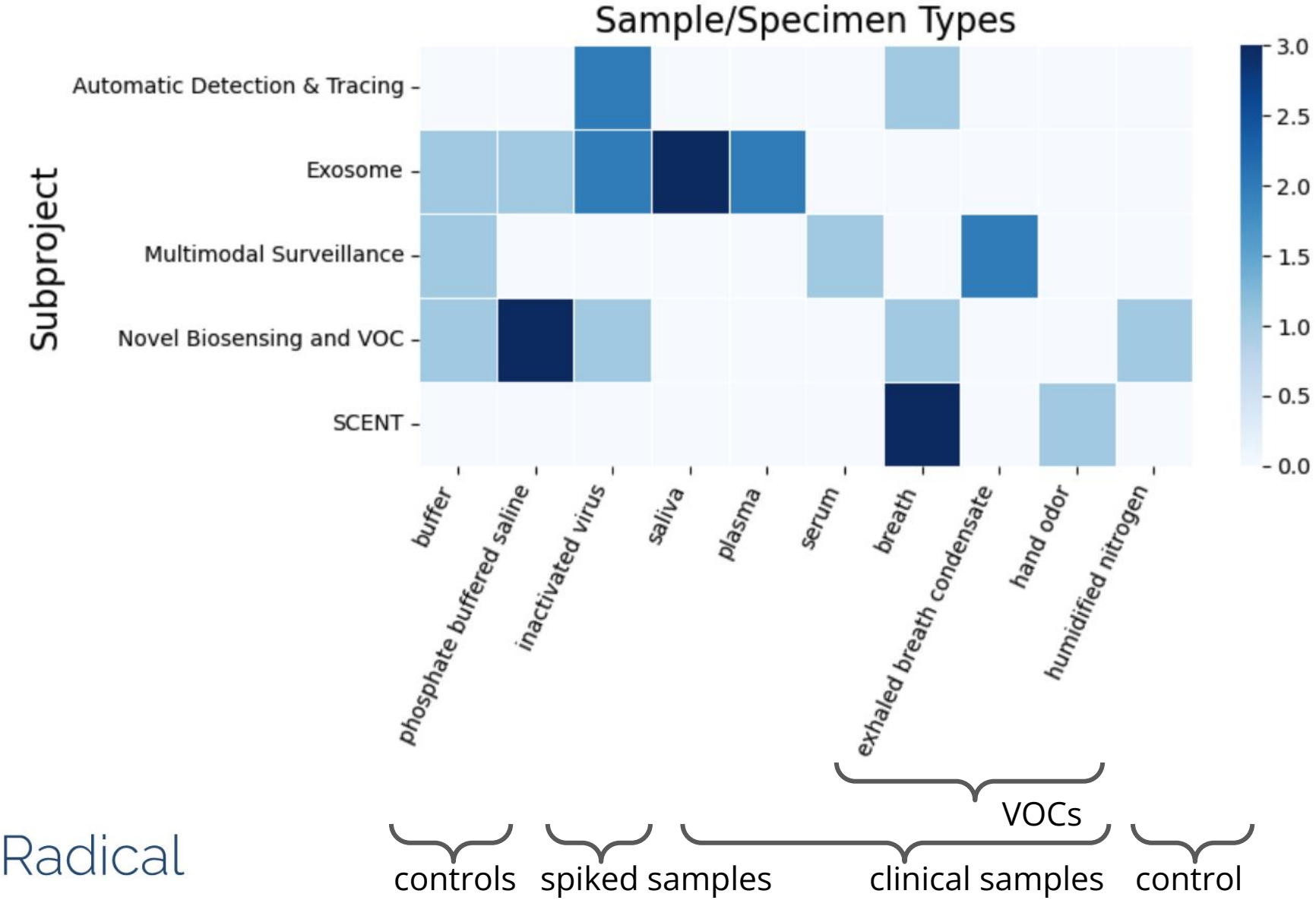

Technology Description
Viral Quality Assurance Panels (inactivated viruses)
Clinical Samples
Spiked Samples (inactivated viruses)
Test Results
Test Results
Clinical Performance Metrics
Analytical Performance Metrics

Distribution of Tier 1 Data Elements (clinical samples)



up to 46 common data elements harmonized across studies

Diverse Sample/Specimen Types for Method Validation



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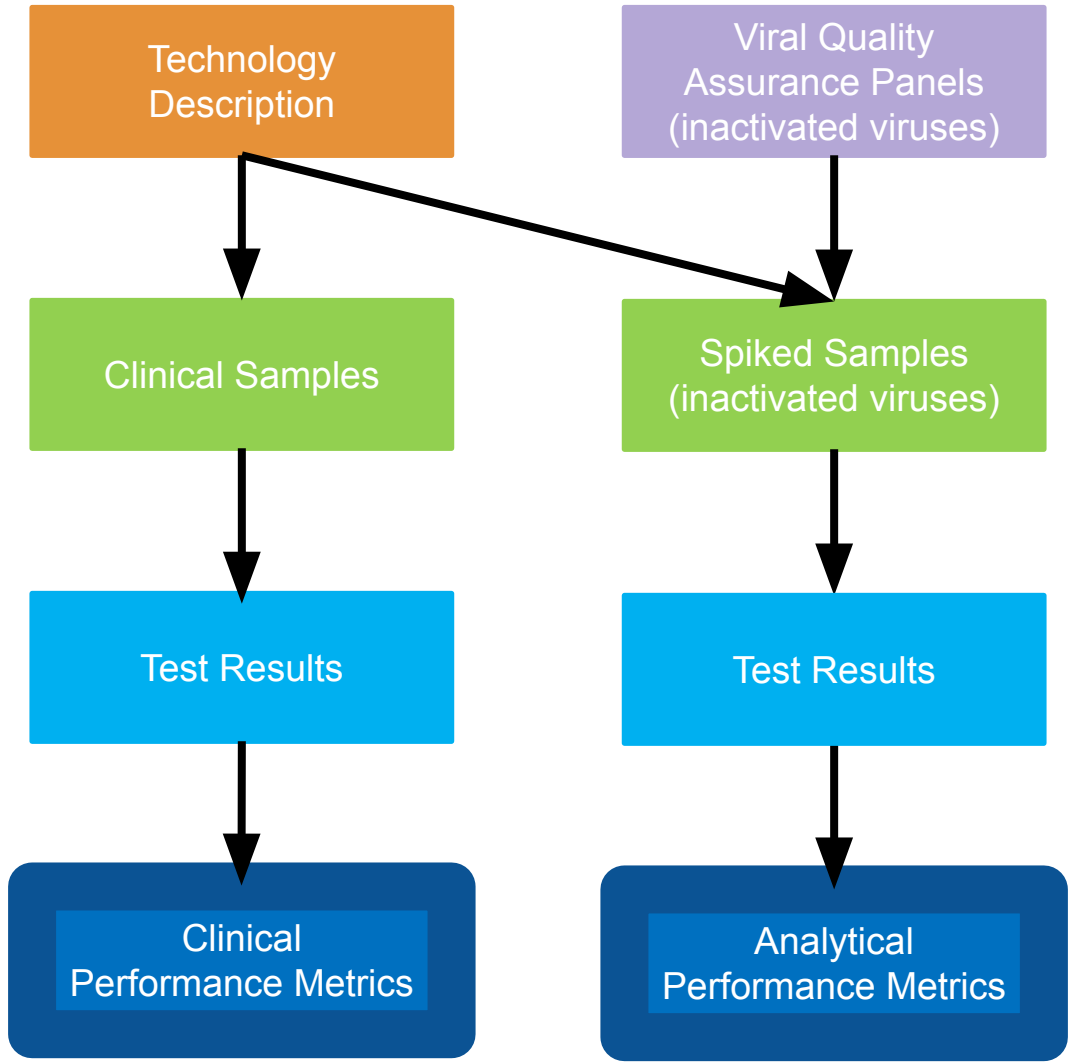
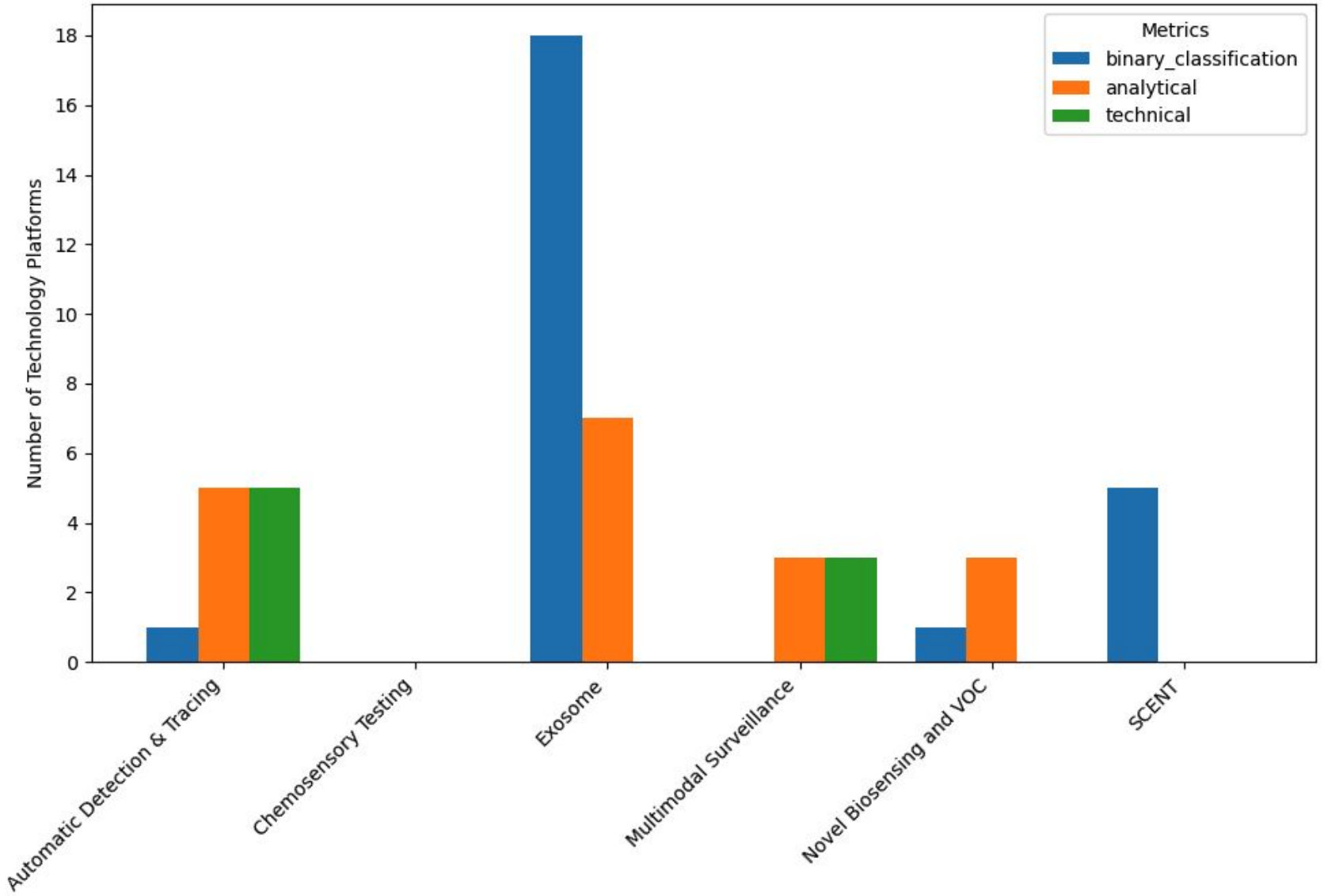
Performance Metrics



Performance Metrics for Diagnostic Methods



binary classification metrics

- sensitivity
- specificity
- predictive values
- percent agreements
- AUC
- ROC curve

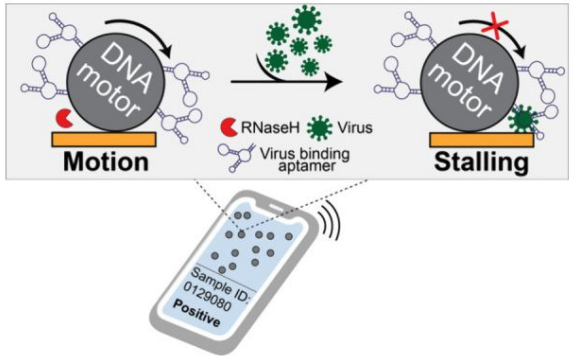
analytical metrics

- analytical sensitivity
- limit of detection
- limit of quantitation
- limit of blank

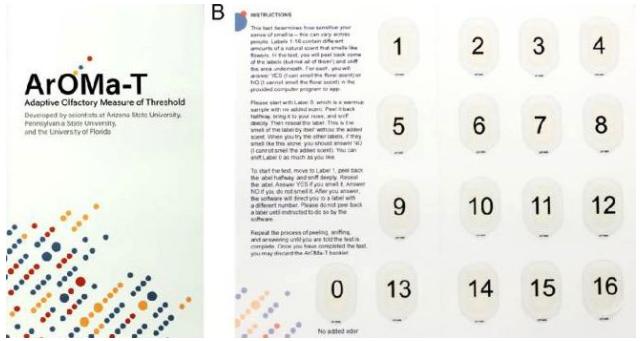
technical metrics

- price per test
- turnaround time

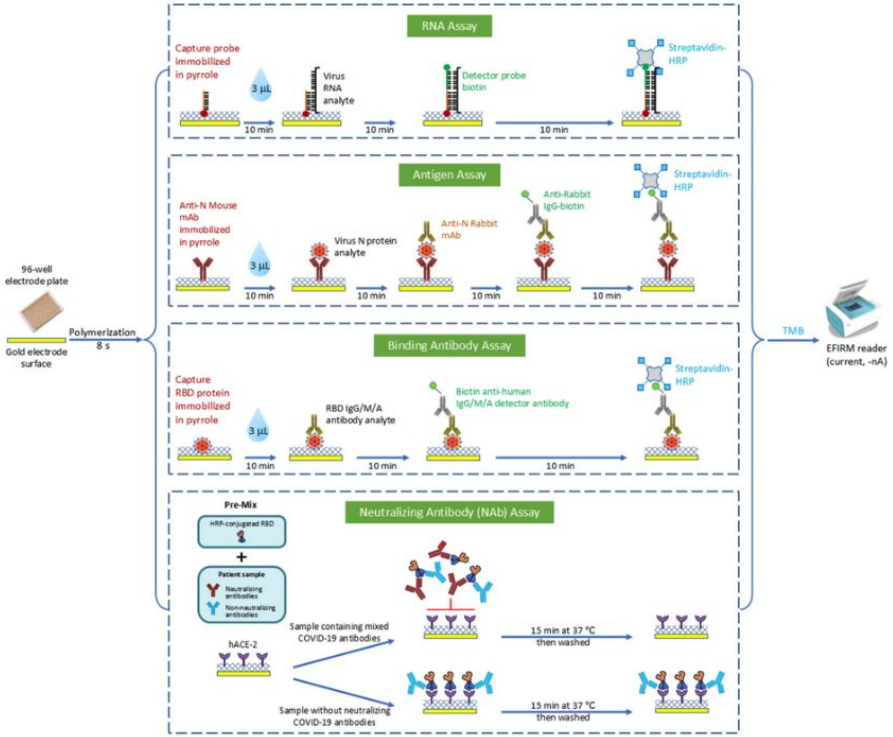
Examples of Novel Diagnostic Methods



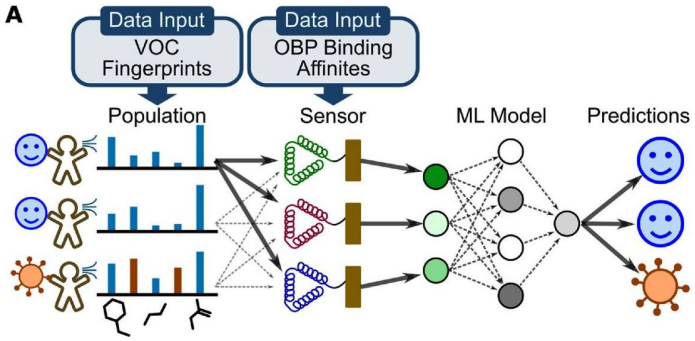
Automatic Detection & Tracing
doi: 10.1021/acscentsci.4c00312



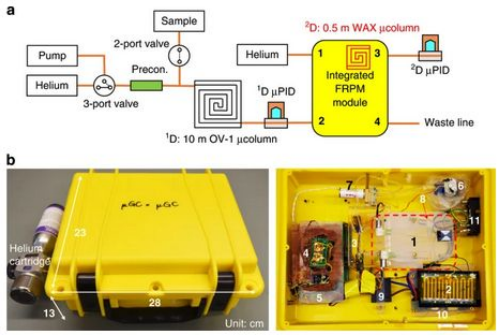
Chemosensory Testing
doi: 10.1101/2022.03.08.22272086



Exosome
doi: 10.1038/s41598-024-81019-4



Novel Biosensing and VOC
doi: 10.1016/j.bios.2023.115237



SCENT
doi: 10.1001/jamanetworkopen.2023.0982

Smart mask

Multimodal Surveillance
doi: 10.1021/acs.analchem.1c02399

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Summary

- The RADx-rad program delivers cutting-edge diagnostic methods, validated across diverse samples and virus variants.
- Harmonized datasets from the NIH Data Hub support real-world evaluation and AI-driven insights.
- The RADx Data Hub provides tools for querying, analyzing, and machine learning in a secure environment.
- Novel diagnostic technologies from RADx-rad are transforming how we can detect infectious diseases—quickly, accurately, and at scale.
- The program's harmonized datasets provide a foundation for validating and deploying future-ready diagnostic and surveillance systems.

Source Code

The source code used to analyze the RADx-rad data and instructions how to setup and run the code in the NIH RADx Data Hub are here:

https://github.com/radxrad/radx-analyzer