



COVID-19 Evidence Accelerator Collaborative

Diagnostics Evidence Accelerator #34

Thursday, July 15, 2021, 12-1 PM ET

Call Summary

Introduction to Diagnostics Evidence Accelerator Meeting #34

This week's Diagnostics Evidence Accelerator meeting consisted of 2 presentations:

1. Challenges in Surveillance Testing – Alan Sachs, Thermo Fisher Scientific
2. Patient Safety and SHIELD – Gregory Pappas, FDA/CBER

As always, thank you to all of the analytic partners, strategic advisors, and scientific advisors that are participating in Project One of Diagnostics Evidence Accelerator.

Challenges in Surveillance Testing – Alan Sachs, Thermo Fisher Scientific

Thermo Fisher Scientific has been supporting customers in many ways to fight the pandemic. The areas where they are providing support are essential lab equipment and personal protection equipment, research and analysis, comprehensive diagnostic testing solutions, and treatments and vaccines. Thermo Fisher has enabled the development of over 270 million tests around the world. This provides them with a unique perspective on surveillance and data capture. They are working closely with FDA/CDRH to understand important testing guidance. They have 7 EUAs for SARS-CoV-2 diagnostic testing and are in the process of converting some to a 510(K) application. One of the premier tests from Thermo Fisher is the TaqPath COVID-19 test. This test targets 3 areas of SARS-CoV-2, but only requires 2 areas of the virus to be detected on the qPCR instrument to be positive. This multitarget design compensates for viral mutations.

The presentation discussed and questioned why testing requirements for SARS-CoV-2 in asymptomatic and symptomatic populations are different. Figure 1 explains the differences in the EUA requirements for symptomatic and asymptomatic tests.

SARS-CoV-2 EUA requirements: Symptomatic vs asymptomatic

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Clinical testing- Requirement	Symptomatic	Asymptomatic
# samples	<ul style="list-style-type: none"> Prospective -OR- archived, 30 positives (~20-25% low positives) 30 negatives Frozen samples acceptable 	<ul style="list-style-type: none"> Prospective (preferred) -OR- archived 20 consecutive positives 100 consecutive negatives
Acceptance criteria	<ul style="list-style-type: none"> "High sensitivity" comparator based on FDA Reference Panel PPA \geq 95% NPA \geq 95% Discordant testing by additional EUA RT-PCR and/or Sanger sequencing 	<ul style="list-style-type: none"> "High sensitivity" comparator based on FDA Reference Panel PPA > 95% (lower 95% CI > 76%) NPA \geq 98% (lower 95% CI > 95%)
Collection criteria	<ul style="list-style-type: none"> All comers NP preferable (OP, NS allowed) 	<ul style="list-style-type: none"> All comers NP preferable, Nasal (both nares) allowable
Other	<ul style="list-style-type: none"> Provided as part of the EUA prior to authorization 	<ul style="list-style-type: none"> Can be provided as part of post market commitment <i>Intended use would initially state that the test requires serialized testing as a mitigation of not having the asymptomatic data</i>

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Figure 1: EUA requirement for symptomatic and asymptomatic test.

In a study published by [Yang et al.](#), saliva samples from asymptomatic individuals were taken and tested for the virus using a qPCR. The investigators converted the Ct value to viron/mL using a standard. The viral load for these asymptomatic individuals were compared to the published viral loads in saliva for symptomatic (hospitalized) patients, and they were very similar. The study by [Lennon et al.](#), showed similar results using nasopharyngeal swabs. Therefore, the viral distributions are the same regardless of a patient being symptomatic or asymptomatic. Thus, the question that needs to be asked is why are there different requirements for registering tests for the symptomatic and asymptomatic populations?

The presentation also discussed the use of qPCR-based genotyping for rapid surveillance of SARS-CoV-2 variants. Figure 2 shows the definitions for variants.

SARS-CoV-2 Mutation vs Variant vs Lineage

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Variant of Concern (VOC) vs Variant of Interest (VOI) vs Variant of High Consequence (VHC)

- **Mutation:** Error introduced during viral replication
- **Variant:** Genome that contains a particular set of mutations
- **Lineage:** All descendants of a branch of the phylogenetic tree

<https://outbreak.info/situation-reports/caveats>
<https://www.cdc.gov/coronavirus/2019-nCoV/cases-updates/variant-surveillance/variant-info.html>
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- Variant of Interest (VOI)**
 - Phenotypically changed as compared to a reference isolate with established or suspected phenotypic implications
 - Identified to cause community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries
 - Also called Variant Under Investigation (VUI)
- Variant of Concern (VOC)**
 - Increase in transmissibility / detrimental change in COVID-19 epidemiology
 - Increase in virulence / change in clinical presentation
 - Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics
- Variant of High Consequence (VHC)**
 - Demonstrated failure of diagnostics
 - Significant reduction in vaccine effectiveness
 - Significantly reduced susceptibility to multiple therapeutics
 - More severe clinical disease

Figure 2: SARS-CoV-2 mutations, variant, and lineage definitions.

Figure 3 shows the combination of technologies that enable the identification and characterization of Sars-CoV-2 variants.

Identification & characterization of SARS-CoV-2 variants

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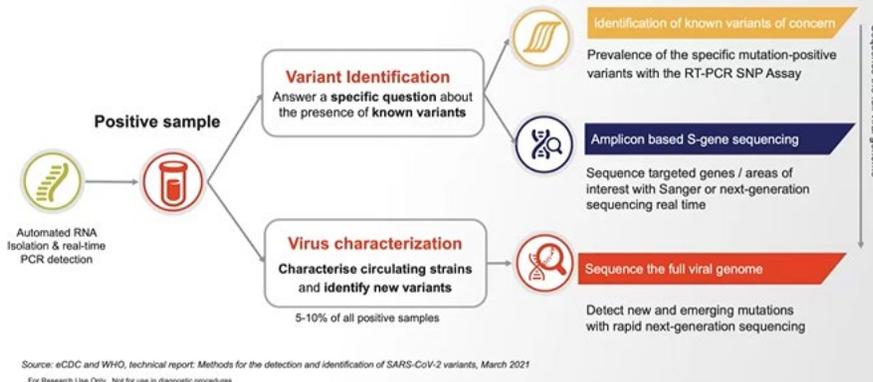


Figure 3: Identification and characterization of SARS-CoV-2 variants.

One of the earlier SARS-CoV-2 variants, B.1.1.7 (Alpha variant), had a 6-nucleotide deletion in the S gene, preventing TaqPath from amplifying the S gene target. Due to the two other targets that the test detected, the test could still detect a positive result, therefore not impacting the test sensitivity. Positive samples that were completely missing the S gene amplicon were presumed to contain the Alpha variant. University of Birmingham was able to use this information to monitor the variant and the impact that it had on the UK population. Thermo Fisher is continuing to rapidly build qPCR assays to support researcher genotyping based on NGS data. The most efficient way to conduct surveillance of known variants is to have a menu of verified real time PCR assays to build a custom panel.

The presentation also discussed a potential proposal for a common database to serve the needs of multiple stakeholders in the US. Figure 4 shows how the data is currently handled in the US.

How is data handled today?

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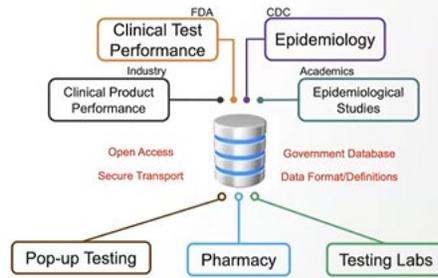


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Figure 4: Depiction of how data is handled today.

However, this prevents many researchers from accessing the data that is needed to conduct the different analyses required to understand disease. Therefore, figure 5 is a proposal that could allow better access to the data for surveillance for future pandemics.

How could data be handled to maximize its value?



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Figure 5: Depiction of how data can be handled.

From the Chat Box

- If there are requirements, what should the requirements be for EUA? Is the default symptomatic most appropriate?
 - Since the data shows similarity in the symptomatic and asymptomatic testing, then the requirements for symptomatic testing can be leveraged for asymptomatic testing.
- How are you ensuring the LIS results to the first downstream entity (PH) in this case using FHIR is a CLIA compliant lab report of record. Not aware of any LISs with capability to provide CLIA compliant FHIR reports.
- Danaher has also discussed similar data access needs to look at performance with their platforms.

Patient Safety and SHIELD – Gregory Pappas, FDA/CBER

There are many use cases where innovation is being held back by a problem with the data. These use cases are patient safety, Clinical Decision Support (CDS), epidemiology/ outbreak monitoring, healthcare research and innovations, public health reporting, regulatory decisions, and signal detection.

There are three types of interoperability: semantic, syntactic, and institutional. FDA primarily works on semantic interoperability with everyone in the ecosystem working with HL7 and FHIR. There are many interoperability challenges and a range of current uses and barriers in health care data. Currently, medical claims data is used routinely, with labs counting as the “low hanging fruit”. In the near future, FDA is looking to add provisions that factor in the use of remote monitoring measurements interoperability. A major barrier in data collection is psychiatric care data interoperability.

Figure 6 shows why we should focus on lab data. SHIELD (Systemic Harmonization and Interoperability Enhancement for Laboratory Data) is the last stop for lab problems. They do not have authoritative source for coding since there are many codes that can be used, therefore, each lab is responsible for using the appropriate code for specimens. This problem has been well documented for over the last decade and is a continuing problem.

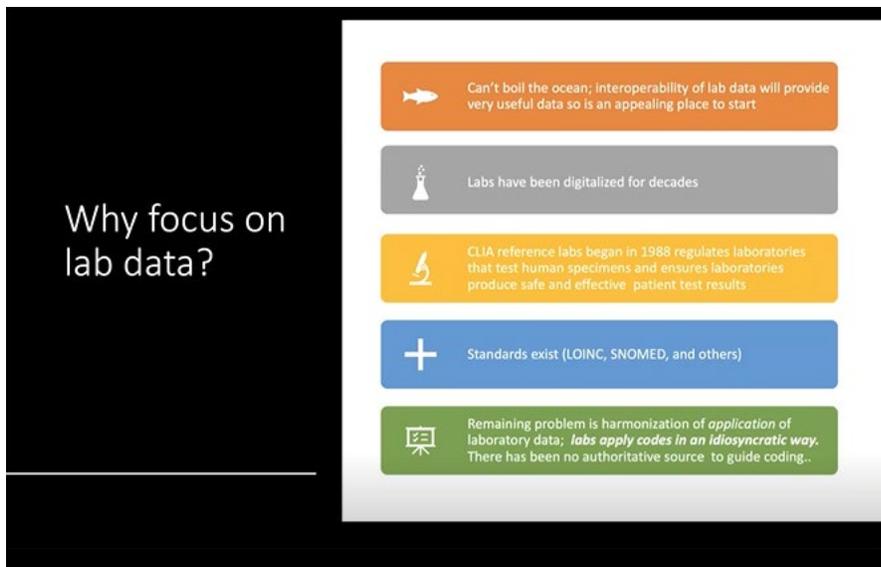


Figure 6: Reasons to focus on lab data.

[SHIELD](#) emerged five years ago out of multi-agency workshop held in 2015 and 2016. The mantra and goal that SHIELD follows is “describing the same test the same way, every time”. They operate under FDA Data Standards Advisory Board (DSAB) and have received funding from multiple sources. SHIELD provides an authoritative source for coding by working with over 70 stakeholders including the government, private sector, and coding organizations.

Figure 7 describes the workflow and data collection process that SHIELD takes when identifying test codes that are used to detect results. The codes are housed on the LIVID file on the CDC website.

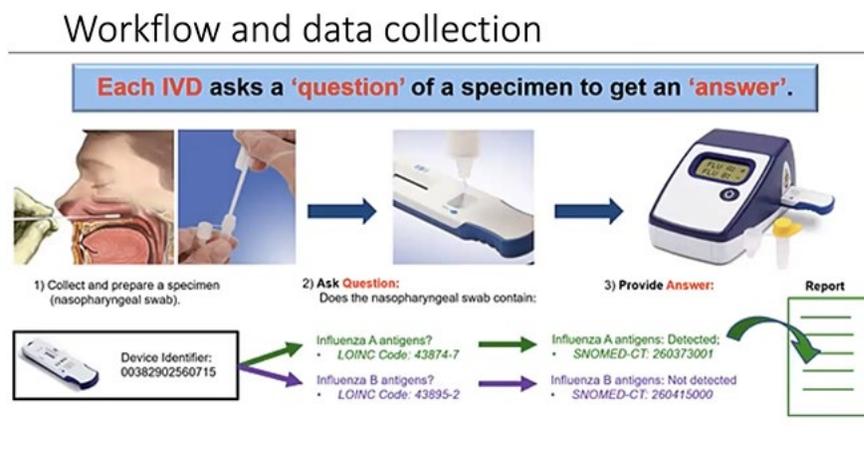


Figure 7: Workflow and data collection process taken to identify lab codes.

During the pandemic, Congress asked the HHS Secretary to solve the problem of coding. The Secretary turned to SHIELD to provide authoritative coding during the pandemic. This [requirement](#) went into effect on August 1, 2020 to help provide crucial information needed to monitor and fight the pandemic nationally. This requirement is a crucial step forward in establishing a national database.

SHIELD is working on building on the response to the pandemic to promote interoperability beyond COVID-19 testing. They published a white paper calling for a strategic plan and have established a planning process (launched on May 4, 2021) that is being led by Micky Tripathi, PhD, the HHS National Coordinator for Health Information Technology (HHS/ONC). The planning process will deliver a clear articulate strategy with a business case that outlines the impact of the strategy and a roadmap of supporting activities during the five-year strategic plan. Figure 8 shows the chairpersons that are involved in the process. If anyone in the Evidence Accelerator community is interested in participating in a committee, please reach out to Dr. Pappas or another member on SHIELD.



Introduction of Committee Chairpersons

Committee	Chair(s)
Coordination Committee	Wendy Rubinstein (FDA) Micky Tripathi (ONC)
Communications/Training/Education Committee	Stan Huff (Logica) Molly Polen (AACC)
Strategic Alignment Committee	Micky Tripathi (ONC) Colin Shepard (CDC) Sara Brenner (HHS/FDA)
LIVD File Expansion Committee	Wendy Rubinstein (FDA) Riki Merrick (APHL) John Snyder (NLM)
Implementation Committee	Scott Campbell (UNMC) Hung Luu (CAP)
Tooling, Technology and Knowledge management	Keith Campbell (VA) Andrew Sills (Deloitte)
Industry Committee	Serge Jonnaert (IICC) Ed Heierman (Abbott)
Effectiveness Committee (Monitoring and Evaluation)	David Baorto (Regenstrief) Vaishali Patel (ONC)

Figure 8: Committee members for the Strategic Plan.

Next Steps

- Continue making data connections through the Evidence Accelerator and through www.EvidenceAccelerator.org.

Next Meeting: Thursday, September 2, 2021 12-1 pm ET