COVID-19 Evidence Accelerator Collaborative

Diagnostics Evidence Accelerator #25

Thursday*, March 4, 2021, 12-1PM ET*

Call Summary

Introduction to Diagnostics Evidence Accelerator Meeting 25

This week's Diagnostics Evidence Accelerator meeting consisted of:

1. Update on the Diagnostics Evidence Accelerator Lab "Retro" (Susan Winckler & Carla Rodriguez-Watson, Reagan-Udall Foundation for the FDA)
2. Guidance on Evaluating Impact of Viral Mutations on COVID-19 Tests and Lessons Learned Thus Far (Tim Stenzel, FDA/CDRH) [Link to PDF]
3. SARS-CoV-2 Genome Surveillance (Brian Krueger, LabCorp)
4. FDA's Data Modernization Action Plan (Ram Iyer, FDA)

As always, thank you to all of the analytic partners, strategic advisors, and scientific advisors that are participating in this project. As of the week of March 1, 2021, we are on step 6 where accelerators are revising Aim 1 manuscript on testing characterization and on step 9 where accelerators are running their Aim 2 analysis.

Update on the Diagnostics Evidence Accelerator Lab "Retro" (Susan Winckler & Carla Rodriguez-Watson, Reagan-Udall Foundation for the FDA)

The readout from the retro lab meeting was provided to the Accelerators. The roses (things that are working) from the Lab meetings include:

- Opportunities for collaboration and networking, the learning opportunities from accelerators, speakers and the FDA that have shaped studies and products development. Also, accelerators appreciated the transparence in data flow, data capture and the methods of presenters. Along with the roses stated for the Lab meetings, Accelerators from the Parallel Analysis workstream appreciated the strong project management that moves the Parallel Analysis forward. Also, the stepwise approach improves analysis along with the Accelerators presentations inform the protocol were something that worked well for Accelerators.

The thorns, or the items that need improvement, that the Accelerators stated are that there needs to be a way to track the topics that have surfaced during the meetings, determine if the relevancy of the topic, and follow up on the topic if it is relevant. Accelerators stated that the shared drive is helpful, however due to corporate, federal government and IT security requirements, it is hard to access the files. Finally, Accelerators agreed that we need develop a unique device identifier.

The buds, or the opportunity that the Accelerators are looking forward to, were divided into 3 categories: convening, situational awareness, and progress against COVID-19. For the convening aspect, Accelerators stated that keeping the Evidence Accelerator ecosystem and apply the framework beyond the pandemic. Also, continuing the interaction and intersections with other groups and digital health organizations to facilitate product development. Additionally, Accelerators are looking forward to increasing their understanding of and further leverage different real-world data set in regulatory studies to increase efficiency in delivering safe products to patients. Finally, understanding incentives to share information and data so that FDA can have view of real world.

Accelerator stated that the Lab meeting allow for situational awareness. Accelerators stated that they will like to see topics such as best rapid tests for public health purposes (not just clinical), trends on SARS-CoV-2 variants and update on surveillance, vaccine effectiveness & impact of variants, testing strategies, trends in mask-wearing and effectiveness, and asymptomatic individuals. Additionally, data interoperability suggestions that accelerators provided are collaboration between health system, public health or other partners to present on mutual benefits and provide a more complete view of the patient, explore 21st Century Health IT, and expand groups to engage Digital Health, international organizations, and other holders of RWD.

Finally, Accelerators are exciting to make progress against COVID-19. Currently, characterizing how testing is being conducted in the real world is being addressed in the Aim 1 manuscript that is being worked on by Accelerators. Also, Accelerators stated that they are excited about solving conflict in real time to deliver solutions to improve public health and centrally calibrate the >1,044 SARS-CoV-2 diagnostic tests in use worldwide.

SARS-CoV-2 Genome Surveillance (Brian Krueger PhD, LabCorp)

LabCorp's timeline and milestones for the development of the SARS-CoV-2 RT-PCR test was shared during the meeting. LabCorp was one of the first commercial laboratory to launch an assay and receive an EUA for testing. Additionally, LabCorp was one of the first commercial labs to receive EUA for at home collections and Direct-to-Consumer testing.

In order for public health experts to respond to the pandemic, it is important to know where the different variants of the virus are requiring an assay that detects the variants. The LabCorp PCR test detects 2 locations in the SARS-CoV-2 genome, both located in the Nucleocapsid (N) protein. The genome sequencing determines the genetic code of the entire virus. Their workflow for viral genome surveillance is first isolating the genetic material from the sample that they receive from the lab. Second, place the sample on a plate for processing. Third, detect the virus using a real time RT-PCR. For genome processing, LabCorp takes the leftover extraction and run the genome sequencing to identify the version of the virus in the positive sample. This allowed them to associate the virus with the position they fell on the virus family tree.

The genome sequencing work at LabCorp started as an internal research and development program. The work began early in the pandemic. LabCorp received a contract from the CDC in December 2020 to continue the work in real-time. Mutations such as S: D614G drive our response (e.g. vaccine and therapeutic development) to the pandemic. The new variants (B.1.1.7, P.1, and B.1.351) have a mutation on the spike protein which makes it more transmissible. Mutations in the spike protein and

receptor binding domain are the most worrisome because a mutation in those areas will prevent our immune system from recognizing the virus reducing immunity

Through the CDC Baseline Study, LabCorp tracks the viruses as they spread, and the results are presented weekly on the CDC SPHERES calls. In order to do this, LabCorp collects samples from their North Carolina facility and condense them into the positive plates to sequence the sample. LabCorp is able to track the virus at the state level through the CDC Clade distribution. This has informed public health experts about the different variants and their emergence in states. Through this effort, LabCorp was able to identify B.1.351 in South Carolina, Virginia, and Illinois. Additionally, they identified a mutation in the B.1.351 variant, B.1.526, which was primarily located in the Northeast region of the country. B.1.526 accounts for 5% of the cases that emerge in New York and New Jersey.

Questions:

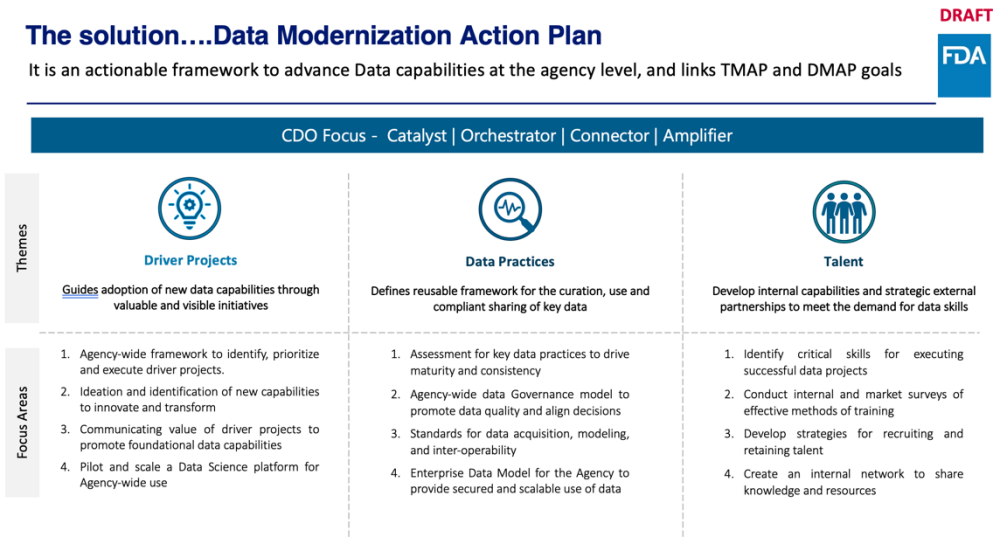
- Is the process for sequencing common across labs that do sequencing? Is that process the rule or the exception?
    - LabCorp is unique in the way that they are extracting for sequencing, however, the process for sequencing is standard across organizations.
- An accelerator asked once variants are detected who do you need as a collaborator to hone in on that region to increase sampling?
    - LabCorp has developed an algorithm internally to allow them to pick the high value samples from the region of interest.
- Is there any ability to link back to testing participants' EMR/claims data, so that genomic and clinical/healthcare resource use data could be integrated?
    - Currently, they are doing work for the CDC. They share deidentified data with the CDC and if the CDC is interested in a particular sample, LabCorp is able to reach out to the state public health agency to conduct contact tracing.
- Do patients give permission on the variant testing and do you tell the patient about the variant?
    - They are testing the residual PCR material. Since this is for research, they have an IRB wavier to conduct this research.

FDA's Data Modernization Action Plan (Ram Iyer, FDA)

Data is an integral to everything that is done at the FDA to advance Public Health. However, the way that the data is collected and shared has changed substantially. The FDA launched five new ways of interacting with data and the ecosystem that will enable science-based regulation of data technologies. The ways are regulatory decision making, interoperable processes, technology and data complexity, real-world data and advanced analytics, and solving the innovation paradigm.

They analyzed how customer experience looks in a well run data organization. Through collaboration with stakeholders, they found that they want easy access to data, data strategy focused on stakeholder outcomes, faster insights, continuous innovation and use of advanced data and analytics technology, internal talent, automated operations, and the ability to share data in a secure and compliant manner.

The solution that they developed is the Data Modernization Action Plan (DMAP). There are three themes for DMAP: driver projects, data practices, and talent. The below figure summarizes the aspects of DMAP.



The next steps for DMAP are communicate DMAP to internal and external stakeholders, form an agency wide Steering Committee to govern data decisions, develop roadmap and schedule for DMAP implementation, identify and staff key workgroups for execution, develop measures and KPIs to track progress, and develop communication and stakeholder engagement plans

From the Chat Box

- An accelerator asked from a patient perspective how do they know about validity of the test they are getting.
- Another accelerator asked will FDA provide a panel of specimens with common major variants.
- A caller asked if there specific challenges including LDTs in the monitoring for sensitivity issues (and what incentives may apply to overcome potential challenges specific to LDTs).
- A participant stated that for serology assays, the difficulty is in getting samples of patients whose infection is confirmed with a variant by sequencing a few weeks after infection. Is FDA looking into partnering with institutions to make such samples readily available?
- An accelerator stated that we also need to understand the clinical features associated with new COVID-19 viral variants. Denmark sequences 50% of the virus isolates and can link them to clinical data to know which variants are associated with particular clinical profiles, a task that requires the maintenance of a high level of clinical data veracity, therefore sequencing alone is not enough.
    - Another accelerator commented that they agree with this. Surveillance for variants has been low in the US. What is FDA doing to help improve variant surveillance? What levers does FDA control that can increase the percent of viral isolates that are sequenced to better understand variant epidemiology?
    - A caller stated that Its $$$. We could sequence a lot more, but I don't want to eat the entire medical center budget, or I'll be out on the street.
- A caller stated without knowing what the variant is at time of diagnosis, it will be difficult to characterize the differences in the immune response for patients later on. Might be critical missing information overall when looking at population immunity responses.
- Another caller asked if we ever found multiple variants in the same patient simultaneously.
    - A participant responded that patients could have viral evolution over time, especially in those with weakened immune system.

- An accelerator asked if patients give permission on the variant testing and do you tell the patient about the variant.
    - In response to this question, an accelerator stated that for surveillance sequencing, the data is not reported back to the patient by design. Those folks are not subject to CLIA regulations, so it is a lot easier to do surveillance than clinical sequencing. What most folks want is clinically reported sequencing data where it can go into the medical record and then be scraped to be analyzed with other properties and tests from the patient.

Next Steps

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

Next Meeting: Thursday, March 18, 2021 12-1 pm ET