COVID-19 Evidence Accelerator Collaborative

Diagnostics Evidence Accelerator #12

Thursday, *August 20, 2020, 12:00-1:00PM ET*

Call Summary

Introduction to Diagnostics Evidence Accelerator Meeting 12

This week's Diagnostics Evidence Accelerator meeting consisted of 4 presentations and discussion.

1. Saliva Direct (Anne Wyllie, Yale School of Public Health)
2. Update on FDA-authorization for the Use of Saliva (Michael Waters, FDA)
3. Data Visualization for Project One (Gina Valo, FDA/OC)
4. Announcing our Project One Diagnostics Accelerators (Susan Winckler, Reagan-Udall Foundation for the FDA)
5. Discussion

SalivaDirect (Anne Wyllie, Yale School of Public Health)

SalivaDirect is a saliva-based assay that received an Emergency Use Authorization (EUA) on August 15, 2020. The research teams' goal is to improve testing options from the nasopharyngeal swab. The reason why they looked into alternate options is due to the swab being uncomfortable to the patient and risky to healthcare workers. Also, the research team did not want to take away resources that healthcare workers needed. Finally, the RNA extraction and the RT-qPCR are expensive to run and labor intensive. The researchers experienced a shortage on supplies for RNA extraction. With the RT-qPCR, they had to run 3 reactions with one sample which was took a longer time. The primers that they were using was N1, N2, and RP. They saw success with the N1 primer which was reliable and stable. The N2 primer was variable which could lead to inconclusive results. The researchers compared the results from the nasopharyngeal swab and saliva. They saw promising results of SARS-CoV-2 in saliva-based samples. There was a higher viral load and a stable detection in patients that used the saliva method compared to the swab.

SalivaDirect is an extraction free and utilizes dualplex RT-qPCR. Suspected individuals expel saliva that naturally pools in the mouth into a vial. Once the saliva is expelled, it is mixed with Proteinase K which breaks down the proteins in the saliva. Next, heat of 95° C is added for 5 minutes to inactivate Proteinase K. Finally, the sample is tested in dualplex RT-qPCR for SARS-CoV-2 N1 and human RNAse P (RP). They found that SARS-CoV-2 detection in saliva is stable without preservatives which is cost effective. The research team conducted spike-in experiments where they took a saliva sample from a heavily positive sample. They created 3 different SARS-CoV-2 concentrations: 12 copies/μL, 25 copies/μL, and 50 copies/μL. They incubated it for 7 days at 4° C, room temperature, and 30° C. They found that the viral load was similar to the load that was seen with the fresh sample. The same result

were seen in the clinical samples. Also, the saliva collection was stable at room temperature beyond 20 days. SalivaDirect maintains sensitivity without the RNA extraction and the singleplex maintains sensitivity with the multiplex. There is a mean of 1.8 count increase without RNA extraction and 1.2 count decrease with multiplex.

They have validated reagents and instruments to use with SalivaDirect with multiple vendors. SalivaDirect cost $1.29-$4.37 for reagents per sample, but with discounts, the cost can be as low as ~$1 per sample. They conducted validation studies using the different reagent and platforms. The graphs looked similar among all of the combinations tested. They have limit of detection of 3-12 copies/μL for all of the combinations which is similar to many of the other PCR tests out there. For their clinical validation, they compared the detection in paired nasopharyngeal swab and the saliva samples by. There was a 94% sensitivity compared to swabs.

The goals of their EUA is to reduce testing cost, increase the number of tests in the community and reduce implementation time to use saliva. The key points of their research is to provide a protocol which can be used by others, not a laboratory-developed test which only their lab could use. They are not manufacturing test kits for distribution, all reagents can be ordered direct from suppliers, helping to keep prices down. They will continue bridging studies extended to all authorized labs and the research team will not be making any profit from developing their methodology. More information on their efforts can be found on www.SalivaDirect.org or by emailing SalivaDirect@gmail.com.

Update on FDA-authorization for the Use of Saliva (Michael Waters, FDA)

There are currently 5 EUA that involve the use of saliva. The ease of access can be beneficial to patients if good results can come out of the EUAs. FDA has made 7 EUA templates available on the IVD EUA website to help facilitate the preparation, submission, and authorization of an EUA. The templates reflect FDA's current thinking on the data and information that developers should submit to facilitate the EUA process. There are 4 validation studies that the FDA recommends be conducted for a molecular diagnostic assay intended to be used to test saliva. Those studies are Limit of Detection (LoD), clinical evaluation, inclusivity, and cross reactivity. Understanding premarket and post market effects with saliva testing are very important. Also, it is crucial to gather RWE to understand this pandemic.

Data Visualization for Project One (Gina Valo, FDA/OC)

A visual presentation of a patient that was tested multiple times for COVID-19 was given. The purpose of the presentation was to illustrate the data being captured from the numerous tests being conducted at different testing facilities. There are a number of data points that are collected through an EHR, Lab Information System, and the instrument. The data that is being captured can shift between being structured and unstructured. As we move from the instrument to the EHR, the fidelity of the data is lost. At the instrument level, the data is structured. However, when the data moves into the EHR, there is a mixture of structured and unstructured data. There is no system that is capturing the full picture since there are different providers and systems that are involved in the data capture. This is the interoperability challenge.

In order to solve this problem, the research community needs to look at one data element at a time. The example that was shown looked at the manufacturer data element. At the instrument level, the data element is structured, however, as we move into the EHR, there are cases where there is no EHR to record the data, the data becomes unstructured, or the data is missing. The goal is to keep the integrity

of the data element through the system and be able to aggregate the data at the patient level. This is what it means to connect the pipes. By using RWD to understand the performance and the limitation of testing, we will gain a better understanding of how to use data for RWE.

Announcing our Project One Diagnostics Accelerators (Susan Winckler, Reagan-Udall Foundation for the FDA)

The first group of participants that will be participating in the Diagnostics Parallel Analysis Accelerator are Aetion/Health Verity, Sutter Health, Harvard/United Health Group, UC Health System, and Health Catalyst. If there are more teams that want to participate, they can reach out to the Foundation.

Discussion

- There is an established way to address using LOINC codes to shuttle data around. Michael Waters of FDA/CDRH suggested that if researchers want to discuss this further, they should reach out to him.
- Need to realize that when the data reaches the EHR, the data will not hold its true form. It will be corrupted during transmission. We need to figure out a way to avoid this because this can lead to lawsuits and litigations.
- It is important to know what data is available on the instrument. Some data that we need to link to the end, may not exist in the same manner at the instrument level. Work needs to be done at the manufacturer level to ensure that the data needed is readily available.

From the Chat Box

- The question of having validation on automated PCR instruments was asked by a caller. The caller stated that the biggest problem many labs are facing is a lack of manpower. A ton of testing capacity is unutilized because there are not enough techs to work, especially during the evening and night hours.
- In regard to the SalivaDirect study, a caller asked if the heating step is for inactivation or is it necessary for extraction.
    - The answer was that it was to inactivate Proteinase K.
- An attendee asked given differences in saliva and persistence of virus in saliva, does the RWE data shed any light on "transmission/infectivity in populations?
    - This is on the list of key questions that researchers hope to be able to address in collaboration with the dx-EA data holders.
- Does the data become unstructured as they go from the LIS to the EHR transmitted from the former to the latter in an image?
    - Answer: Yes, the data may be dropped completely or go to an image or PDF
- It is important to understand what comes from the instruments and is available to be passed through to the end
- A caller stated that there is an additional problem where the source data being transmitted to the end users or to unique patients are frequently corrupted during transmission through the multiple transfer engines (or multiple software packages, e.g. middleware)
- A caller stated that in dealing with extra-EHR clinical information systems in the Cath lab and OR, we have chosen to obtain extracts from them and from the EHR and combine the data in a separate database rather than waiting for the vendors to create interoperability between their systems.

- The connections between records is better within a health network if they have made efforts to create a connected system, but it's not automatic - lots of challenges between software applications, software versions of same applications and setting enablement
- Anatomic Pathology labs send narrative reports, inclusive of histopathology images, in PDFs. For tumor biopsies, the immunohistochemical results are in the PDF, along with the staging information and recommended protocols.
- At clinical reference labs, the lab instruments generally send analytic results to the LIS via a standardized LIMS interface.
- The LIS then sends the lab results data in HL7 v2.x format to the EMR/EHR that submitted the lab order via an interface engine such as Cloverleaf. Error correction prevents corruption.

Next Steps

- If researchers are interested in participating in Project One, they can contact Amar Bhat at abhat@reaganudall.org.
- Continue making the data connection and learn about test performance for the next meeting.

Next Meeting: Thursday August 27th, 2020 12-1 pm ET