



COVID-19 Evidence Accelerator Collaborative

Diagnostics Evidence Accelerator #5

Thursday, *June 25, 2020, 12:00-1:00 pm ET*

Call Summary

Introduction to Diagnostics Evidence Accelerator Meeting 5

During the 5th diagnostic accelerator meeting, we had five presentations followed by a discussion period:

1. Connecting the Data Pipes... Generating RWE About COVID-19 Testing
2. RWE for medical Devices: COVID-19 and Beyond (CDRH/FDA)
3. Office of Surveillance and Epidemiology at the Center of Drug Evaluation and Research
4. Exploring an Initial Test Case in Diagnostic testing (RUF/FOCR)
5. University of California Health System
6. Discussion

Connecting the Data Pipes... Generating RWE About COVID-19 Testing

We are part of large community focused on RWD and RWE to answer questions surrounding COVID-19. The meeting was set up with presenter discussing why it is important to understand RWE and medical innovation of devices. Next, there will be a discussion with Office of Surveillance and Epidemiology at the Center of Drug Evaluation and Research that will link to the work that is being done in the Therapeutics Evidence Accelerator with the work we are doing in the Diagnostic Evidence Accelerator. Finally, we will discuss how the pipes connect with two presentations that will focus on connecting the pipes and answering the questions related to real world performance and diagnostics as our first use case.

RWE for Medical Devices: COVID-19 and Beyond

The potential benefits of real world data sources include an understanding of device performance in the real world environment to inform the benefits and the risks, collecting outcomes that may be challenging in nontraditional way, providing opportunities to partner with patients in new ways for patient reported outcomes, reducing time and cost to answer important questions, and informing future device modifications and new technology development. The ultimate goal is to move to a modern regulatory framework that better aligns evidence generation with innovation cycle using modern technology.

The use of RWE started 10 years ago with the setup of a Medical Device Epidemiology Network which was focused on creating a better infrastructure for RWD and statistical methodology for analyzing data

for RWE. This led to the creation of a national system called the National Evaluation System for health Technology (NEST) which has a governing committee comprised of representatives from different stakeholders. The FDA awarded funding for an independent NEST Coordination Center which is housed in MDIC. There are already 20 use cases that are underway, and several have generated results for use. Since 2015, there have been 65 medical devices that have received marketing authorization based on RWE.

CDRH has provided extra regulatory flexibility for COVID-19 products to get them to market. They have done this through guidance documents and Emergency Use Authorization (EUAs) to ensure that the products are reliable and safe. So far, they have put out 300 medical devices into market to combat COVID-19. With EUA, tests can be developed, validated, and authorized within weeks instead of months or years. The downside is that the FDA is authorizing tests with less evidence and data, so it is important to get a better understanding of how the test performs in the marketplace through RWE. By collecting data, developers are able to see how their product works, make change if necessary, and collect data to keep their product in the market with full marketing authorization. Using RWD and RWE to evaluate COVID-19 diagnostic testing, the diagnostic accelerator will provide important complementary information about real world patterns of use, test performance, and immunity. We can have a coordinated program of diagnostic testing research that uses real world data that generates useful and high-quality evidence that will inform clinical, public health, and policy decisions.

CDRH is working with MDIC who has developed a framework that discusses how to use RWD, develop appropriate designs and statistical methods including modeling to generate RWE for product development and regulatory decision making. CDRH has developed Semantic Harmonization and Interoperability Enhancement for Laboratory Data (SHIELD) which addresses the limitation of lab data inconsistency between different systems and unlinked with clinical data. If two data sets are linked, then there will be a better understanding of test performance. They have developed a mapping tool for LOINC codes with the diagnostic tests for COVID-19.

Office of Surveillance and Epidemiology at the Center of Drug Evaluation and research

They have launched several projects that were discussed under the Therapeutic Evidence Accelerator. One of the projects that they launched is the use of codes used to diagnose COVID-19. The purpose of this project is to identify hospitalized COVID-19 cases using diagnostic codes and validate algorithm based on laboratory test results. They developed a data set on presumed hospitalized cases based on claims data, presence of diagnostic laboratory test, and the result of those tests. The objective was to calculate the positive predictive value for the code-based algorithm using a diagnostic laboratory test as a reference standard. They are going to look at data twice over a 6-month project period to validate the algorithms to recognize change in practices and testing patterns. They are also going to look at data across four different sentinel data partners. To understand the performance characteristics, they need to know which test to use in which setting and the influence of different criteria in different settings. This will be looked at in a follow up project.

Exploring an Initial Test Case in Diagnostic testing

Through the Therapeutic Parallel Analysis Workgroup, there are 6 data sets that multiple partners are working on to develop a common plan to see how reproducible the results are when implementing them on different data sets. This is the goal for the Diagnostic parallel analysis workgroup too. Using the framework that MDIC and others have developed, there has been a guidance developed to start

answering the core questions discussed in previous meetings. The place where this workgroup is going to start to focus on is the individuals that have tested positive for the SARS CoV-2 RNA and align that with antibody test results, including test type, sample type and manufacturer information. Also, it is important to link that to clinical and demographic data. We can overcome the challenge of linking the data points together by working together on this problem. With everyone coming together, the workgroup will be able to do things such as anchoring on viral testing, collect data on serology tests, demographics, clinical outcomes, and symptoms to determine real world testing patterns and how long it takes for total antibody, IgM, and IgG to develop. The core objective we are trying to address is can multiple test be linked to the same individual.

We start with the RNA (+) because, in part, antibody tests were developed to reduce occurrence of false positives. Even though there is a need for understanding the real-world test performance, there is a greater need for an understanding of the sensitivity of the antibody test. More importantly, focusing our effort on a smaller section of data will allow us to better understand how to connect the pipes correctly so that we can add on additional data to enable us to describe a fuller picture of accuracy. A future aim will be to look at long term clinical data and if there will be a need for additional diagnostic testing to better understand long term clinical outcomes and reinfection rates. After this, the goal will be to include individuals that are negative and apply the same principles to see the impact of those results.

University of California Health System

University of California Health System includes UCSF, UCSD, UCLA, UCD, and UC Irvine. All of the data that they extract is from EPIC. UC Health has seen an increase in the number of COVID-19 cases and admissions. There are patients that are admitted to the hospital for other reasons such as surgery and psych that are positive for COVID-19, so not all admitted patients have respiratory issues. They have developed a comparative tool to look at the all of the drugs that are being ordered and administered, and the order in which they are ordered. UC Health has ordered and completed 8098 antibody tests with 7572 negative tests and 466 positive tests. Therefore, approximately 6.15% of the tested were positive for serology. They have approximately 1500 patients that have completed a PCR test and also completed an antibody test. They have many patients that are doing many different PCR and antibody test. Anytime a patient shows up to the hospital will get a PCR test, so the timing of when the tests were done is going to affect the results and the number of tests done for an individual is going to vary.

Discussion Points:

- We need a better system to collect and understand RWD and RWE and its impact as we move into flu season since it may put individuals at more of a risk.
- We need to collect more data as we build and connect the pipes for COVID-19.
- Given the number of EUA, there are going to be tests that we will not have data for. We will have data for national labs but not smaller labs running the tests. Therefore, the question of how do we gather the data on tests that have a small testing volume? The solution that was presented was to ask all labs to collect data since the performance characteristics of point of care testing will be different.
- It is important to think about the outcomes that we are measuring with the tests, therefore seeing the longitudinal data is important.
- When collecting data, we have to keep in mind that there are multiple tests being used, therefore, data collection will vary.

- We cannot compare the results globally because every country has different protocols in place for controlling COVID-19.

Comments from the Chat Box:

- It is important to know whether the patients are symptomatic or asymptomatic since coding can be variable.
- It is important to understanding the prevalence of the infection in different countries so we as a research community can move forward to combat COVID-19. This point led to a discussion of why we need to look at prevalence. A point that were brought up was that prevalence could skew the false positive results. An important question that was raised was how we can collect the data surrounding this idea.
- The idea of understanding how we can calibrate the results by using a universal test for each type of test, and the use of positive and negative controls was raised.
 - Currently there are approximately 200 molecular, antigen, and antibody test in use in the US and 703 used across the world.
 - It will be difficult to collect data for all of the tests, so it will be helpful to have a universal test used for data collection.
- When health systems are testing for COVID-19, they are conducting multiple tests that may be days apart. Test are conducted every time a patient is going to the hospital to ensure that they are not positive for COVID-19, therefore, patients could be getting the antibody test first and then PCR test or vice versa.
- It is important to have a unique code for each type of test, manufacturer, and version. Any manufacturing changes should be counted as a new test.
- The data issues and complexities, combined with all the other complications mentioned, can make using the information seem impossible. We as a workgroup can avoid that conclusion and think about what we need to know that will teach us how to use the data going forward to match data for its intended use.
- For diagnostics, following patients across health systems becomes more important to answer some of the crucial questions surrounding COVID-19.

Next steps:

- Move forward with the test case to connect the test results, test manufacturer, clinical data, and demographic data.
- Continue the discussion of using sensitivity and specificity of the test during the next meeting.

Next Meeting: Thursday July 2nd, 2020 12-1 pm ET