COVID-19 Evidence Accelerator Collaborative

Diagnostics Evidence Accelerator #28

Thursday, *April 15, 2021, 12:00-1:00PM ET*

Call Summary

Introduction to Diagnostics Evidence Accelerator Meeting 28

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

1. Heidi: A Story of Data Interoperability (Gina Valo, FDA)
2. Front Porch Chat with Micky Tripathi, HHS National Coordinator for Health Information Technology
3. Decoding the T-Cell Response to SARS-CoV-2 (Lance Baldo & Thomas Manley, Adaptive Biotechnologies)

As always, thank you to all of the analytic partners, strategic advisors, and scientific advisors that are participating in Project One. As of the week of March 29, 2021, Accelerators are on step 6 where they are revising Aim 1 manuscript on testing characterization and on step 9 where Accelerators are running their Aim 2 analysis.

Heidi: A Story of Data Interoperability (Gina Valo, FDA)

The Hypothetical Patient "Heidi" was previously used as a model to understand the importance for connecting the pipes for real-world performance of diagnostic tests. Since the first Emergency Use Authorization (EUA) was granted for vaccines, similar challenges arise in the vaccine space. In this hypothetical scenario, Heidi becomes eligible for her COVID-19 vaccine in February 2021. She receives her first dose at a pharmacy and her second dose at a mass vaccination site. In April 2021, she feels ill, but is negative for COVID-19. However, she tests positive for flu at her primary care physician's office.

Then, in April 2022, she is seen by her primary care physician and is positive for COVID-19 despite being vaccinated. Given Heidi's health care journey, she has created various data point in the data system. The data points created are shown to the right.

When looking at just one site (e.g., primary care physician's records), the data collected do not tell the complete story of Heidi's health
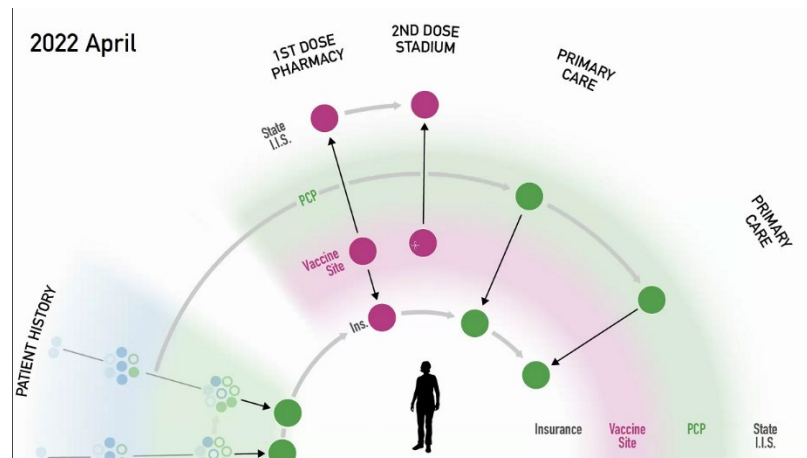
record. Therefore, it is important to develop ways to look at the complete journey that Heidi has been on since the beginning of her health record to understand the data.

There are many questions about data interoperability that still need to be answered. How can we connect specialty COVID-19 vaccine registries that are separate from the IIS system and how to get the different state systems to talk to each other? The challenge is to make sure that we understand the data sets, their strengths and weaknesses, and the kinds of questions that each data set is able to answer.

The Evidence Accelerator community is invited to speak out if they have data that can answer the critical question about the vaccines.

"Front Porch" Chat with Micky Tripathi, HHS/ONC

Dr. Micky Tripathi, the National Coordinator for Health Information Technology (ONC) in the US Department of Health and Human Services, joined FDA's Principal Deputy Commissioner, Dr. Amy Abernethy, to discuss data interoperability. The following questions and answers have been paraphrased.

Dr. Abernethy: Can you define data interoperability from your perspective?

Dr. Tripathi: The standard definition is two or more systems that are exchanging information and using the information that is exchanged. The piece that I like to add to the definition is that there is exchanging of information so that the information is used and appropriate to the use case. Many people believe that interoperability is binary, either you have interoperability or you do not. However, there are different types of interoperability. Additionally, the idea that data can be in one place is not possible in every scenario. Therefore, interoperability is a multilayered concept that is appropriate to the need and having it standardized to be used for multiple use cases is essential.

Dr. Abernethy: This team has been analyzing the real-world performance of COVID-19 diagnostic tests. They have been collecting data about the person being tested, testing circumstance, sample, the diagnostic test, the performance of the diagnostic test, manufacturer information, and the testing machine. This information has to flow. From your perspective, what should we think about as we try to improve the flow of the relevant data element from the diagnostic testing space?

Dr. Tripathi: We first need to recognize that data is a byproduct of a clinical or business process. Therefore, data quality issues are related to the lack of alignment between the process that is generating the data upstream and what the goals and uses are. The second thing is healthcare delivery is fragmented. For example, there are 43% of labs are done in hospitals, 33% are done in commercial labs, and 11% are done in physician offices. There are no rules for the lab industry to develop an interoperable system (i.e., couple of labs coming together to develop a common system) like there is for other industry. Even though this is a tough task, it is something that can improve interoperability. The third thing for labs and diagnostics is that this is a complex value chain. Therefore, quality issues become compounded as you move down the chain. If you can achieve standardizations upstream (e.g. LIS system), then a source of the challenge is solved. Additionally, the source of monitoring downstream is essential to get the sources of data upstream to agree to the standards. In order to accomplish this, we need to think about what is the problem that we need to solve and how are we going to get it aligned.

Dr. Abernethy: ONC recently finalized the requirements for interoperability. Can you speak to the requirements and how you think they may affect the real-world data space and are there parts to the end-to-end value chain that you think will be impactful?

Dr. Tripathi: ONC has regulations for labs that are in the certification of the EHR system. ONC works with industry to identify nationwide standards that are needed and then require EHR systems to adopt those standards. There are different standards that are core datasets which includes test types, values, and results. This means that EHR systems are required to handle the data if it is sent to the EHR even as LOINC code and make it available to other places. ONC does not have the ability to tell EHR vendors what to do with the data. They only have the ability to tell EHR vendors to keep the data as they receive it.

Additionally, the Federal government (i.e., FDA, CDC, NIH) has a huge role to play in this since the health system is fragmented on the private sector side. It is difficult for the private sector to solve the fragmentation without the help of the federal government. The private sector will have a role to establish, monitor, and reinforce the system. There were rules placed previously that had to be pulled back due to clinician burden, therefore there are ways that the federal government can lead in the end-to-end coordination of industry. ONC is making this a priority to address since the business community can self-organize around and it is essential for the federal partners to help out.

Dr. Abernethy: One of the ways to solve a problem is how to innovate your way out of a problem. Has ONC been thinking about what kinds of innovations they will like to see in this space and where we can go with interoperability in the future?

Dr. Tripathi: One thing we should be think about is what do we need to standardize and what we do not need to standardize. With new technology, there maybe some things that we do to need to standardize given the new algorithmic approaches used. Additionally, bringing in additional data that may help us solve the problem should be considered. For example, getting more granular data for race and ethnicity and adding more social determinant of health data to documentation requirements can be helpful. However, there is a clinician and patient burden by adding this. If we think about the opportunities to evaluate what we know from other datasets such as demographic data from payors can help inform the types of data we want to evaluate. In doing this, there are issues such as privacy issues, therefore we have to be careful when we are considering the additional data. Additionally, we should think about why we need the data to inform what actions we need to take. In terms of innovations, we need to think about multiple levels of interoperability. We can leverage nationwide interoperability networks. Finally, FHIR and FHIR-based API should be leveraged for exchange.

Dr. Abernethy: We have discussed the role of government and the role of providers, but what do you believe is the role of industry and EHR vendors in advancing this space?

Dr. Tripathi: They are critical partners in this process. When people think of HIE, they think of state and local HIE, however, the nationwide networks are doing a lot. The nationwide networks are developed by the EHR vendors and ONC works with them collaboratively.

Dr. Abernethy: Could we hear your top three 'do now' ideas?

Dr. Tripathi: One is thinking about what you are doing to standardize things. If you aren't doing anything, then why? The second is how are you encouraging your partners to exchange data in a

standardized way. The third thing is to embrace FHIR and FHIR-based solutions. The fourth thing is making available EHR which is supposed to be the designated record set, however, there is no expectation that it will be standardized. Therefore, we need to think about how to address non-standardized data. In conclusion, we need to start thinking about how to make data available now.

Decoding the T-Cell Response to SARS-CoV-2 (Lance Baldo & Thomas Manley, Adaptive Biotechnologies)

T-cell response plays a critical role in eliciting an immune response. Even though researchers were unclear as to why this was, T-cell response provides an early indication of infection before the development of antibodies. T-cell response rises as early as 2 days post diagnosis and peak after 1-2 weeks. Additionally, the response persists more than 100 days post infection.

The ImmuneCODE database was created by Adaptive Biotechnologies and Microsoft and made freely available to the world. The database consists of over 6,500 samples from 20 global collaborators from 7 countries. Researchers performed analytics on those samples and identified approximately 10,000 viruses specific TCRs which can be used for clinical test. Also, they performed *in vitro* mapping on the receptors associated with SARS-CoV-2. Through this process they created the ImmuneCODE database, a T-cell diagnostics assay, and tools and data to measure vaccine response, and an immunoSEQ T-MAP COVID which allows for visibility into cellular immune response to vaccines.

In the earlier T-cell receptor sequences mapped across virus, the researchers identified both class I and class II antigen assignment. Additionally, the methodology developed can be used to evaluate blood samples of individuals prior to the emergence of SARS-CoV-2 and be compared to the individuals that have COVID-19. This allowed the researcher to analyze the shared signals between the two groups and the SARS-CoV-2 specific signals.

T-Detect COVID is an FDA EUA-authorized test that Adaptive is using. T-Detect identifies individuals with an adaptive T -cell immune response to SARS CoV-2, indicating recent or prior infection with SARS-CoV-2. Both from days from diagnosis and days from symptom showed a PPA above 90% and the NPA was 98.7% in the secondary analysis and 100% in the samples collected prior to December 2019. Additionally, the researchers looked at the PPA days post diagnosis and compared it to the serology tests that were available on the market. T-Detect COVID assay performed better compared to the other serology tests as the days since diagnosis increases.

In the analysis of T cell response from Vo' Italy, the researchers found that the response correlates with neutralizing antibody titers. This is important because the CD4+ response is what is driving antibody development. In the replicate finding from Vo' study showed strong association of CD4 signal only with neutralizing antibody titer. The researchers also looked at the data set from the Seattle. They evaluated the T-cell data and compared it to two antibody tests to understand the trajectory of the antibody signal. They found that the T-cell response is higher in more symptomatic or severe cases. Additionally, the researchers looked at the longitudinal analysis of T-cell responses and compared it to the serology test that are currently in the market. From this analysis the researcher saw the signals that distinguish the T-cell data from the serology data, is reflected in the later time frames and shows a clear distinction in the non-hospitalized patients.

T-cell test identifies individuals not captured by other measures of response. In the data, 68% of individuals that tested negative with neutralizing antibody test were positive with the T Cell assay.

Variants also impact infection and vaccination. With the T-MAP annotation of T-cell receptors to antigen locations, the researchers can assess how the common sites of immune response are affected by different variants. Adaptive is participating in active research programs. The programs are characterization of vaccine-induced T cell responses in vulnerable populations such as cancer patients and patients with autoimmune diseases, particularly those on immune-suppressing medications. Additionally, Adaptive is conducting research in the Long COVID (PASC) space.

From the Chat Box

- An accelerator noted that if Heidi dies at home, we would not necessarily be able to link her death with the rest of her records which is a challenge with interoperability.
- Another accelerator mentioned that in addition to data being a byproduct, it's also generated with a certain lens. For instance, for billing purposes, so using it for research comes with risks and biases.
- We currently have over 1,100 covid-19 diagnostic tests worldwide that are not centrally calibrated - we are fighting a pandemic and need to understand the predictive value of each one of those tests.
- An accelerator suggested that we need to build prototypes with real data to test the interoperability.
- We are still facing problems with laboratory taxonomies such as LOINC and laboratory in-vitro diagnostic (LIVD) codes that are not yet optimized for automated implementation, and for facilitating the integration of findings across instruments that generate equivalent results using different methods.
- Do the nationwide networks get IIS data?
  - An accelerator responded that it is their understanding that the national networks get that data from the same sources (i.e., vaccine registries / state HIEs) that submit to IIS.
  - One accelerator was wondering how the data that goes from a stadium site to IIS would get to Epic's CareEverywhere.
- Race, more specifically impacts of racism, are important in health outcomes. However, it can be difficult to gather information (especially reliably reported) data on a person's race in a commercially insured setting. Is there a role for the federal govt to play? Much like they do for race data available for Medicare patients?
- Another issue to consider is what happens if we actually succeed in creating truly interoperable clinical data and hospitals/clinics and labs have access to all of their patient's data? Right now, HIPAA defines a patient's "designated record set" as:
  - A group of records maintained by or for a covered entity that is:
    (i) The medical records and billing records about individuals maintained by or for a covered health care provider; [or]
    (iii) Used, in whole or in part, by or for the covered entity to make decisions about individuals.
  - This brings up the issue that if a patient requests all of their records used by a CE in their decision making on that patient's care, does that CE include the external data made available through interoperability? How does a clinician document that they used this data? Who is responsible to getting back to the patient?
- An accelerator stated that they pushed their vaccine info into Epic through to their PCP. She stated that it will be super if we could shift to embracing patient reported data in the process.
  - An accelerator mentioned that pediatric vaccine data are often handled differently than data for adults.
  - Another accelerator was wondering if a site like a stadium is using Epic. What types of systems these locations are using?

- Are there dependencies by geography on reporting to IIS? Illinois for example requires HCP reporting within 72 hours to IIS. It might vary by state given the way the vaccine is coordinated for distribution.
- Dynamics differ at the state/HIE/vendor/exchange level. In Maryland for example, (it is my understanding) the data flow from the mass vax site to the state registry (i.e., ImmuNet) then either directly to provider networks (e.g., MedStar/Hopkins) or indirectly via an HIE (i.e., CRISP). Commonwell (Cerner/others), Carequality (Epic/others) and eHealth Exchange (including federal participants) have agreements that enable exchange of these data at several levels within this process - though access policy differs by purpose (treatment vs public health) and cohort
- What is the T cell data showing on fully vaccinated individuals who go on to get infected?
- How can we start thinking how to use T-Cell (with or without other info) to describe immunity from vaccines vs. natural infection?

Next Steps

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

Next Meeting: Thursday, May 6, 2021 12-1 pm ET