



## **COVID-19 Evidence Accelerator Collaborative**

### **Diagnostics Evidence Accelerator #18**

*Thursday, November 5, 2020, 12:00-1:00PM ET*

#### **Call Summary**

##### **Introduction to Diagnostics Evidence Accelerator Lab Meeting 18**

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

1. NBA's COVID Testing Strategy (David Weiss, National Basketball Association; Christina Mack, IQVIA; and Yonatan Grad, Harvard T.H. Chan School of Public Health)
2. Decoding the T-Cell Response to SARS-CoV-2 (Lance Baldo, Adaptive Biotechnologies)
3. UHG Covid-19 Testing Strategy Simulator (Natalie Sheils, United Health Group)

##### **NBA's COVID Testing Strategy (David Weiss, National Basketball Association (NBA); Christina Mack, IQVIA; and Yonatan Grad, Harvard T.H. Chan School of Public Health)**

The National Basketball Association developed a protocol that governed the restart of basketball in Orlando, FL. There were no positive tests among the players and team staff after arrival quarantine in Orlando, FL. The NBA also tested people who came into contact with the players such as flight attendants and bus drivers. Their arrival process consisted of a 2-day quarantine period with two negative tests (following several weeks of testing in home markets). The Orlando operating dates were June 24, 2020 through October 12, 2020. There were 16 testing locations and approximately 6,000 individuals tested. There were daily PCR testing for all living on the Disney Campus and 2-3 times per week testing for most of those living off-campus and working at Wide World of Sports and the hotels. The labs they worked with were BioReference Lab and Quest Diagnostics, using tests primarily from Roche and Hologic. There was also some secondary use of a limited number of point of care tests. Manufacturers that provided tests were Cue, MesaLab, Visby Medical, Quidel, and Cepheid. Also, the NBA supported community testing where they donated tests and provided free testing to people in Orlando directly and through Florida Health. They have participated in a number of COVID-19 research and internal assessments with Columbia University, Yale University, Sanford University, University of Central Florida, Cleveland Clinic, Mayo Clinic, and IQVIA.

The NBA put best practices into place to keep the number of COVID-19 cases low. They analyzed data daily, looked at the sub population, and actively managed the diagnostic testing program to keep the community safe as possible. RWE is essential in the setting of emerging infection and newly approved diagnostics, and drove continuous evolution of overarching NBA protocols. Beyond testing, the NBA was looking at the physical surrounding, practical contact tracing, and monitoring and incentivizing testing and compliance. The Roche machines used provided a cycle threshold (Ct) value which helped them understand how much of the virus is in the sample. The population that they were analyzing was

primarily a healthy and young population; however, there were individuals, among Disney staff and transportation drivers for example, who had COVID-19 and recovered. As they were going through the program, there were continuous discussion about the lessons learned from the tests and Ct values and how to apply the lessons learned to keep their population healthy and safe.

One of the lessons learned were that during the viral proliferation the tests are not able to pick up the virus right away, therefore they increased their quarantine when possible for post arrival to 7 days. The change in CDC guidelines encouraged the NBA to change their approach to quarantine. They also learned that they will have to distribute their population into 2 subgroups: 1) Individuals recovered from SARS-CoV-2 Infection and 2) Individuals with acute SARS-CoV-2 Infection. All individuals were given a serology test and PCR test. The key takeaways from the viral shedding among recovered, “Persistent positive” individuals were that individuals experienced negative PCR tests following clinical recovery, prior to additional positive tests and approximately 50% tested positive on a daily PCR test at least once >30 days after initial infection. The observed that the intermittent detectable SARS-CoV-2 RNA for up to 68 days (mean 31), however, the follow-up period didn’t extend past 90 days for most individuals in Orlando. On average, Ct values were above the SARS-CoV-2-specific target limit of detection of 32.7. The persistent positives had a mean of 34.1 and range of 30.3 to 36.7 and acute infection had a mean of 30.84 and a range of 21.4 to 35.5. With the persistent positives, the transmission rate was 0.

From the NBA study, researchers are able conduct a prospective, longitudinal quantitative testing. The research conducted is further discussed in a preprint called [Viral dynamics of SARS-CoV-2 infection and the predictive value of repeat testing](#). The course of the viral infection is very important. There is a value in repeat testing for tests that have low sensitivity as a way to do surveillance and screening. For the NBA study, they were able to estimate the full viral trajectory. The workflow included receiving the clinical sample, conducting the RT-qPCR test, getting the raw data, fit the raw data to a model where they get the proliferation phase and clearance phase, and be able to distinguish between acute and persistent infection. They were able to analyze data from 68 individuals (from both the pre-Orlando period and Orlando period) where 46 had acute infection and 13 reported symptoms. The quantitative tests can inform clinical and public health decision making. The individuals that had symptoms took a longer time to clear the virus compared the individuals that did not have symptoms. By using the Ct value, the researchers are able to estimate whether an individual is in the clearance phase or proliferation phase. Harvard has developed a website where they have used the data from prior to and during the NBA Bubble to estimate how well strategies to test attendees for one-time events (such as games and concerts) work to screen out infectious individuals.

### **Decoding the T-Cell Response to SARS-CoV-2 (Lance Baldo, Adaptive Biotechnologies)**

This presentation discussed using the adaptive immune system to detect and treat disease, decoding the T-cell immune response to COVID-19, application of a T-cell assay, real world experience in Vo’, Italy, and the implications for COVID-19. The immune system detects and treats most disease in the same way. The immune cells (T cells and B cells) trigger a targeted immune response to find, eradicate and remember the threat for a more rapid response to future encounters. The reading of the immune system guides us in advancing diagnostics, vaccines and therapeutics. The immune system diversity is created via DNA recombination of the T-cell receptor genes.

Researchers read T-cell receptors to determine the type of threat that they may have faced. To do this, the lab will take a sample of blood, look at gDNA, use quantitative PCR to amplify the variable region of all T-cell receptors in sample, and use next generation sequencing to sequence all receptors in the

sample. Next, they put the sample through an analysis pipeline to identify and quantitate unique receptor clones and compare that to the patient's immune repertoire. Finally, apply a disease related algorithm to identify if the patient had the disease. T cell are the first cells to respond in the immune system. In their research, they pick up a T cell signal early in an individual's response to infection. In the data they have seen that the T cell response is still present 100 days after initial infection.

The [ImmuneCODE](#) database was created by Adaptive Biotechnologies and Microsoft and made freely available to the world. The database consists of over 5,500 samples from 20 global collaborators from 7 countries, including parts of Europe, Asia and the U.S. They performed analytics on those samples and identified approximately 5,000 virus specific TCRs. 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, including magnitude and duration of response, as well as inform vaccine development. The key takeaways from this growing database were that there were 57 immunodominant epitopes seen from 18 different common HLA alleles (14 from Surface Glycoprotein ("Spike"), 12 from ORF1ab, nd12 from Nucleocapsid Phosphoprotein) and the ability to distinguish between primary infection and vaccine response.

In a study that was conducted in Vo', Italy, Adaptive Biotechnologies collaborated with the University of Padua and Ospedale San Raffaele in Milan to compare the results from the T-cell assay to serology. In the 2200+ subjects tested, there were 70 that were positive, 24 asymptomatic cases and 46 symptomatic cases. The sample collection began 56 days after the last PCR test and was conducted over 3 days. They found that the sensitivity in the PCR-positive tests samples was 97% in the T-cell assay compared to 77% in a commercial IgG test. The specificity was similar in both (98.9% in the T cell assay and 98.0% in the IgG test). They also found that a T-cell score (a measure of clonal breadth and depth) at convalescence, was associated with disease severity. In conclusion, RWE generation and synthesis is pivotal to identifying correlates of immunity and protection. To gather the best RWE, we need diagnostics that are traceable, accurate, and reproducible. T cells are a missing puzzle piece helping to inform immunity and durability.

### **UHG Covid-19 Testing Strategy Simulator (Natalie Sheils, United Health Group)**

UHG developed a tool called [COVID-19 Testing Strategy Simulator](#) that accompanies a paper that they wrote called [Identifying Optimal COVID-19 Testing Strategies for Schools and Businesses: Balancing Testing Frequency, Individual Test Technology, and Cost](#). The reason why the calculator was developed was to provide the community a tool to understand how testing can impact their community. There is a simple calculator and a detailed calculator that provides additional variables that researchers can look at. Some of the variables that researchers can look at are population size, test variables, community prevalence, frequency of screening, and disease parameter. There is a discount rate for pooling. They are adding symptom tracking into the tool. This tool will be used as a way for someone to decide what type of test will work for them, cost, and symptom track which will be different for every population. If someone is administering a test that has low sensitivity, then this tool will allow that person to evaluate how often they can administer that test.

### **From the Chat Box**

- An accelerator asked if the presenter can discuss the distribution of age/ gender/ race/ etc? I'm guessing if it included a large number of players then the population skewed healthy and male?

- We would expect that persistent infection would have higher CT scores compared to acute infection (assuming that means closer to exposure/infection start) given inverse relationship between CT and viral load. Can you tell us if the difference between 30 vs. 34 CT score is meaningful?
  - There was no statistical difference but there was a meaningful difference since the sample size was small. They did have individuals at a high Ct value since they are doing daily testing.
- How did you determine if chronic positives were infectious?
  - They took a conservative approach since they did not have data on a positive test prior to coming into the Bubble. Since they were doing daily testing, they were able to catch people at a high Ct value, however, that did not distinguish what type of infection they had. Therefore, they treated all the cases as an acute infection, contact traced, and isolated.
- Did you continue daily testing on those with acute infection?
  - Yes, when they were infectious. They did not continue testing when the individual recovered. There were also individuals that were lost to follow up, so they do not have data on those individuals.
- Can you provide a ballpark estimated cost for this entire program (testing, contact tracing, isolating etc.)? I'm wondering what it would cost to replicate this for another group, such as university.
- Per your answer to the question about infectiousness of persistent positives, while the CT score suggested infection, did the qualitative result corroborate or did the qualitative result show as "negative"?
  - Often the rerun did not show positive as the Hologic test was not as sensitive as a test to detect those low viral loads, especially among the persistent individuals.
- An accelerator asked that some patients report intermittent symptoms in post COVID recovery. You had some patients test negative and then positive. Any correlation of test with intermittent symptomatology?
  - The presenter responded stating that the recovered patients did not experience renewed symptoms, which was a qualification to ensure that it was likely viral shedding and not an active infection. In some cases, we did not yet have serology, antibodies may not have been detected, and/or there was not a known or proven prior infection. That full picture was critical.
- Were there any extremely high outliers (low Ct/high viral load) that may give us potential info on super spreaders?
  - The presenter responded by stating they did not have active cases or infection spread in the Orlando cohort, we were not able to look at super spreaders.
- Have you tested the cellular immune response before and after the patients were receiving potential COVID-19 treatments such as famotidine?
- An accelerator stated that they have not studied pre/post samples for treatments like famotidine yet. They see many expected effects on T cells from steroidal therapies (immune compartment contracts) and we see changes in T cell fraction (lymphopenia) along disease course routinely as many others have reported.
- An accelerator agreed that T cell will be able to inform and underutilized - fascinating research.
- Do you have any data on "long haulers" i.e. individuals with prolonged symptoms post COVID and any defects in their T cell repertoire.

- The presenter responded by stating that they are attempting to gather data on long haulers.

**Next Steps**

- Continue making data connections through the Evidence Accelerator.

**Next Meeting: Thursday, November 19<sup>th</sup>, 2020 12-1 pm ET**