COVID-19 Evidence Accelerator Collaborative

Diagnostics Evidence Accelerator #16

Thursday, *October 15, 2020, 12:00-1:00PM ET*

Call Summary

Introduction to Diagnostics Evidence Accelerator Meeting 16

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

1. COVID-19: Why we must use the Ct value And what we're losing when we don't (Michael Mina, Harvard School of Public Health)
2. Testing Strategies for Containment (Rob Califf, Paul Varghese, and Menachem Fromer, Verily)
3. Connecting the Dots (Gina Valo, FDA)

COVID-19: Why we must use the Ct value And what we're losing when we don't (Michael Mina, Harvard School of Public Health)

Cyclic Threshold (Ct) values are an important tool. The Cepheid, Roche, and Hologic assays provide a Ct value, however, the Abbott IDNOW assay does not. Multiple literature has shown the importance of Ct values. Ct value is inversely proportional to the viral load. The distribution of the virus between the time that people are infected or clearing the virus verse the infection peak can vary by 8 or more orders of magnitude. The information gained through this can be used clinically. If a patient has a high viral load, then the patient should be isolated. However, if a patient has a low viral load, then it is harder to evaluate if the patient is becoming more infectious or less infectious. As a patient become more infectious with the viral load has a short window of time where they have a low viral load.

Ct values provide useful clinical information. For example, if a patient is tested has a Ct value of 37 and a retest a day later shows that the Ct value is 38, then the patient is clearing the virus. However, if a specimen had a Ct value of 38 and their retest specimen has a Ct value of 24, then that patient is infectious and should be placed in isolation. In a recent study, there was a loss of confidence in the rapid molecular assay called Abbott IDNOW assay when the results showed a sensitivity of 50-60%. This led the FDA to release a statement stating possible test accuracy concerns. In the presenter's opinion, there was a failure to look at the Ct values which affected the results. In the sample, Ct values above 38 were missed. When the Ct values greater than 40 are removed, then the sensitivity will increase to 90%. When the Ct values greater than 38 are removed, then the sensitivity will increase to 95%. Failure to address Ct values had led this assay to be discredited among physicians and researchers. There was a letter written to editor to explain the findings, however, it was desk rejected by the editor.

The Ct value can be used for public health purposes by providing vital information such how long a patient should stay in quarantine, be isolated, or contact traced. This can cause a false negative for the

test, but the patient can be in the post transmissible test. If there is an understanding of viral test kinetics and how tests perform, then the data gathered from these tests can be used to make public health policy. In another study, clinicians and public health officials only saw positive results, however, 50% of the tests had a Ct value greater than 35, most tests had a Ct value above 30, and there were a few results that had a high viral load making them transmissible. Patients that had a Ct value above 35 were not infectious, therefore, the Ct values were not utilized to inform who should be in isolation.

Viral load and epidemic dynamics can be used to optimize pooled testing in resource constrained settings. The understanding of Ct values distribution can be used to understand the prevalence of a pathogen. Ct value data can help to reduce the number of tests required while achieving accurate information on the test. A pooling for prevalence estimation for known positive prevalence across all samples showed that there was a 1% prevalence rate. For prevalence estimated from the 48 pooled tests, they say that the rate was 0.087 (0.52%-1.37%). Therefore, the distribution of the Ct value is crucial for understanding the prevalence.

Ct value distribution can be used to predict epidemic trajectory by evaluating the number of cases. When the cases are increasing, there are more people that are recently infected, therefore, increasing the viral load in patients. At the decrease of an epidemic, the patient population has been infected for a longer period, therefore, there are patients will have a lower viral load. This information can be inputted into a mathematic framework and evaluate the distribution of the epidemic. They used surveillance data from Massachusetts to test this hypothesis and saw that the data confirmed their predictions. In conclusion, Ct values are powerful tools.

Testing Strategies for Containment (Rob Califf, Paul Varghese, and Menachem Fromer, Verily)

Since April 2020, Verily has been supporting COVID-19 response for states, healthcare institution, employers, and university where they have performed more that 1 million tests. Verily set up a tool called Healthy at Work/School which assists in safe reopening. It provides institution's ability to signal work eligibility status, provides an app for symptom screening and test scheduling, and provides analytics on impact of community and workplace prevalence on diagnostics, screening, and surveillance testing strategies. The lessons they learned thought implementation are that employers want actionable recommendations from testing results especially how to bring their employees back to work. Their focus tends to be on cost of individual test and the time it takes to receive the initial results. Also, there is lower awareness of significance of test results and its dependence on prevalence.

The conversation with their customers tends to be about positive test results and what the role of the diagnostic testing is as a reactive test and the types of tests that should be used such as the "Gold Standard" PCR test. Also, the limitations of the PCR test are discussed. The conversation that they want to have is the proactive approach where screening and surveillance testing is conducted as a continuous measure of prevalence in the community. Verily customers always ask how they can use cheap and quick tests. Specificity and prevalence is one of the key elements for a real time outbreak surveillance. In their study with the Abbott test, they saw that if the prevalence of disease is 0.10%, the PPV of the test for disease is 6.10% and the expected positivity rate is 1.60%. As the prevalence of disease increases to 10%, the PPV increases to 87.8% and the expected positivity rate increases to 11.06%. This is only when the sampling is done randomly. Therefore, at low prevalence, specificity tends to lead to majority of false positives. However, real-time aggregate statistics still inform in deriving prevalence, individual antigen results are reported back to individuals, and individual positives are followed up with PCR.

In lower prevalence settings, sensitivity plays a minor role compared to prevalence and specificity. One key issue is specificity deviating from that value reported by vendor, then interpretations may change. In order to solve this, the use of aggregate deployed testing results to re-estimate specificity with real-world evidence (RWE) can help. The second issue is the economic and logistics of testing. Currently, the antigen and pooled PCR test are close in price. There are a lot of tests that are being administered. To be able to accommodate 50 million tests per month, there will have to be a sampling, distribution, and data aggregation scheme developed that will enable the use of RWE of test specificity that inform interpretation of positive test and local estimate of prevalence. This could be done through a random or weighted sampling approach.

Connecting the Dots (Gina Valo, FDA)

If knowing Ct values and understanding real world test performance informs strategy, then we will need to be able to address the following concepts:

- Figure out how Ct value data can flow through existing systems
- Connect a positive antigen test with a positive PCR test and/or diagnosis at the patient level
- Be able to look at testing regimens over time for a given patient
- Understand which test was performed to glean sensitivity and specificity for use in strategic models.

From the Chat Box

- A caller stated that the Hologic Panther methods do not provide Ct values.
    - This was clarified that this only pertains to the isothermal TMA assay. Hologic does have a Panther Fusion assay which is a qPCR. But additionally, even with the TMA version, they can be transformed into quantitative loads.
- A participant stated that CT values differ based on assay parameters, so if you took the same exact sample and ran it on two different assays, you will likely see variation in CT value. Additionally, the total allowable error of PCR is plus or minus 3 CTs, so a 1 CT shift is considered to be within the margin of error of the test.
- A caller asked how much variation is there in Ct values for different tests, in different labs, etc.? Is the Ct value most informative to clinicians who understand their own labs standards?
    - The presenter responded that this is true. 1) if possible, the methods can be calibrated to individual labs / instruments based on their empirical distributions. Additionally, we have found that the within-individual variation in viral loads over the course of an infection greatly exceed the variation across labs / instruments and so they have found that even without calibration by lab/instrument the methods are quite robust.
- Regarding the presentation, a caller asked if we should be focusing on both sensitivity and specificity together to evaluate the operating characteristics?
- A caller asked what data supports relationship between infectiousness and CT values?
- A caller asked if the contact tracing study provides evidence on low Ct values are less infectious?
- A caller shared a paper that goes against the grain that high Ct's are non-infectious https://www.medrxiv.org/content/10.1101/2020.06.10.20127837v1.full.pdf
    - A caller stated that the paper is from human data out of Spain; they found 1/5th of mild COVID patients had culturable virus with Ct's >31, and about 1/3rd of severe patients with Ct's >31.

- A caller asked 1) Is there variation by country in max Ct value for positive? 2) to what extent does process of sampling/swabbing effect the Ct count?
- A called stated that random 1000 people on the street is not representative of the community unless everyone were on the street.
    - Another participant stated that random 1000 people on the street is not fully random. He said "on the street" in gest. We just need some idea of a fairly random group. For example, outpatients getting screened is a good group to use. Many different options.
- A caller stated Ct value equals cycle time of the PCR amplification for the various gene targets. lower value is more virus. Neutralizing antibodies is the body's response and not a direct measure of the virus.
- Accelerators have (thus far) not captured CT values in their CDMs. How can we get this data flowing?
    - A caller stated that the accelerator will need specific samples. We discussed a while ago that the ACORN study has Ct values, but we don't have antibody tests. So, to find cohorts/data sources with all of this is difficult.
- A participant stated that there is a potential opportunity to incorporate CT values, or realize their value post EUA regulated environment.
    - Another caller stated that EUA and Ct values are separate issues. For public health, it certainly has no impact. For clinical use - physicians can use these values. The assays are thus far not approved for quantitative values - but their nature, they are quantitative. Clinicians currently are using this information "offline" regardless of how the tests are authorized. That is a clinical decision that is allowable. Even if not authorized for reporting in the medical record.
- If anyone would like to visualize these VERY important ideas of false positives in a low prevalence population and understanding different testing strategies (pooling, sensitivity, specificity, frequency, etc.) you can check out a calculator we recently released: https://calculator.unitedinresearch.com/complex_dashboard
- A participant stated if the values are being used for clinical use, it is better for clinicians to understand their own lab. This is always the case with clinical laboratory values. It's why we give reference ranges for labs/instruments. for essentially all clinical assays. So, the important point is that this is not a new problem to laboratory medicine.
- Another called stated that we might be able to have more exposure outside the EUA environment in the future, since converting from EUA to a cleared test will carry a different level of performance burden to obtain that clearance. We could think about how to harness the information to better inform decisions or community trends.
- An accelerator stated that we need to focus on specificity. The accelerator was giving a talk about Ct values, but specificity is also absolutely crucial. I think that for antigen tests for example, we need orthogonal rapid tests and algorithms similar to the CDC HIV algorithm.
- Are there number of specimens in a pool reported to providers/public health for decision making?
    - The presenter stated that currently pooling is not really being done very much. We could be pooling hundreds of tests together with relatively little loss. The strategies would need to be understood to put these methods to use.
- A caller stated that "community" has different meanings based on how it is used. In Massachusetts, 60%+ of early cases were related to long-term care facilities. Some communities with prisons look like hot spots but virtually all cases were limited to the prison. Some college

campuses are hot spots with cases focused on the campus. All this is different than screening outpatient population or people walking down the street.

- A caller asked if we should be concerned with cost-effectiveness in concert with costs?
- A caller stated that the major problem with pooling is LABOR. It's not easy to find a bunch of certified lab techs to pool 1000's of samples each day. If pooling could be automated, then you would see it used A LOT more.
- Another caller stated that the reimbursement framework for pooling is complex. And limited cost effectiveness in areas of moderate or high community spread. Samples would need to be retested and potentially double charged, also taking more time as well
- A caller stated that there are 7 FDA EUAs with 2 different pooling approaches, but not all are reported currently. the caller presented at the LOINC meeting on the encoding approaches as we look to provide laboratory's guidance on reporting in concert with ELR and HHS requirements.
    - Another caller stated that at some point the current EUAs will be converted... that is the opportunity to include the additional data.
- A caller stated that the FDA is no longer consider additions or new EUA submissions for LDTs. Now it's up to each lab to create their own LDTs with medical director oversight.

Next Steps

- Continue making data connections through the Evidence Accelerator

Next Meeting: Thursday, November 5th, 2020 12-1 pm ET