



January 21, 2021

Dear Health Commissioner or Director,

It has come to our attention recently that some state departments of health are requesting that clinical and public health laboratories report cycle-threshold (Ct) values with SARS-CoV-2 polymerase chain reaction (PCR) test results. We are writing to voice our concerns about potentially inappropriate use of Ct values with COVID-19 testing and to provide further information regarding the more appropriate scientific interpretation of Ct values obtained by PCR-based nucleic acid amplification methods. The American Clinical Laboratory Association (ACLA) is the national trade association representing leading laboratories that deliver essential diagnostic health information to patients and providers. ACLA members are at the forefront of driving diagnostic innovation to meet the country's evolving health care needs and provide vital clinical laboratory tests that identify and prevent infectious, acute, and chronic disease. The Association of Public Health Laboratories (APHL) works to strengthen laboratory systems serving the public's health in the United States and globally. Our nation's public health labs are an essential component of the U.S. public health system and are America's first line of defense against a wide range of health threats. Clinical laboratories work closely with public health laboratory partners to provide surge capacity testing during public health emergencies, and collectively, ACLA and APHL members have performed millions of diagnostic tests since the start of the COVID-19 pandemic.

As you may know, there are several different types of diagnostic tests to detect the SARS-CoV-2 virus that causes COVID-19 infection. Real-time PCR is one type of test that works by amplifying the nucleic acid of the SARS-CoV-2 virus present in a patient specimen. The total number of amplification cycles required to reach a threshold for a positive result in a PCR test is defined as a cycle-threshold (Ct) value. To date, all COVID-19 PCR tests that have received Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) are qualitative tests, meaning that they are authorized to report a positive or negative result only.<sup>1</sup> In contrast, quantitative PCR tests are specifically designed to measure the level of viral material by comparing the Ct value of the specimen to the Ct values of reference samples that are run in parallel. There are currently no commercially available FDA Emergency Use Authorization designated quantitative tests for SARS-CoV-2 RNA in the U.S., and further data and standardization of test methods would be necessary to develop such a test.

In an effort to aid in the prioritization of COVID-19 cases with higher viral loads and potentially higher transmissibility, some state departments of health in recent months have requested that clinical laboratories report Ct values along with SARS-CoV-2 qualitative RNA test results. However, **current scientific evidence and federal health agency guidelines urge caution against the use of Ct values from qualitative tests to inform case investigation, patient management, or public health surveillance efforts.** In a November 13, 2020 FAQ, the U.S. Centers for Disease Control and Prevention (CDC) stated that Ct values from COVID-19 tests can be “interpreted as positive or negative but cannot be used to determine how much virus is present

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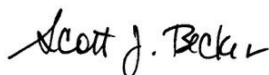
<sup>1</sup> In Vitro Diagnostics EUAs (30 Dec. 2020), available at <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas>

in an individual patient specimen.”<sup>2</sup> Similarly in a December 10, 2020 FAQ, FDA stated, “[T]here is no consensus as to whether or not particular Ct values correlate with a person being or not being infectious or risk level for disease severity. So, appropriate care should be taken with interpretation of Ct values.”<sup>3</sup> Numerous pre-analytical and analytical factors unrelated to the amount of virus in a specimen may influence a SARS-CoV-2 RNA PCR test’s Ct value, such as collection method, time of collection after onset of infection, storage and transport methods, number of primers and probes, nucleic acid target, extraction method, amplification method, and instruments used.<sup>4</sup> A December 29, 2020 FAQ from the College of American Pathologists noted, “Ct-values are not standardized across specimen sources, testing platforms, or laboratories. Although Ct-values have been correlated with prognosis and infectivity in some studies, there is an opportunity to over-interpret results or attribute false precision to a Ct-value.”<sup>5</sup> Furthermore, Ct values can vary substantially among different PCR-based methods depending on how the assay was designed, making comparison difficult among the hundreds of SARS-CoV-2 PCR tests that have received EUAs in the U.S.<sup>6</sup>

As your state considers requirements for laboratory reporting of SARS-CoV-2 RNA PCR test results, **we urge caution against the potential misuse of Ct values for case investigation, patient management, or public health surveillance efforts. As noted above, there is currently no scientific consensus to support the use of Ct values for these purposes.** Additional clinical research is necessary to better understand how Ct values may play a role in COVID-19 testing in the future, but this research should be conducted in an academic setting and should not impose a greater reporting burden on laboratories that are already overwhelmed by various customized data requests from public health entities throughout the pandemic emergency. As a practical matter, it is important to note that some manufactured test kits for which FDA has granted an EUA are incapable of extracting Ct values.

Thank you for your consideration of our concerns. APHL and ACLA are committed to continuing to partner with you to combat COVID-19 in your state.

Sincerely,



Scott J. Becker, MS  
Chief Executive Officer, APHL



Julie Khani  
President, ACLA

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<sup>2</sup> Frequently Asked Questions about Coronavirus (COVID-19) for Laboratories (3 Dec. 2020), available at <https://www.cdc.gov/coronavirus/2019-ncov/lab/faqs.html#Interpreting-Results-of-Diagnostic-Tests>

<sup>3</sup> COVID-19 Test Uses: FAQs on Testing for SARS-CoV-2 (12 Dec. 2020), available at <https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/covid-19-test-uses-faqs-testing-sars-cov-2>

<sup>4</sup> APHL Ct Values: What They Are and How They Can Be Used Version 1 (9 Nov. 2020), available at <https://www.aphl.org/programs/preparedness/Crisis-Management/Documents/APHL-COVID19-Ct-Values.pdf>

<sup>5</sup> College of American Pathologists Cycle threshold (Ct) Values Questions & Answers (29 Dec. 2020), available at <https://documents.cap.org/documents/cycle-threshold-ct-values-questions-and-answers.pdf>

<sup>6</sup> D. Rhoads, DR Peaper, RC She, FS Nolte, CM Wojewoda, NW Anderson, BS Pritt. Caution must be used in interpreting the cycle threshold (Ct) value. Clin. Infect Dis. (2020), available at <https://doi.org/10.1093/cid/ciaa1199>