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Critical Aspects of SARS-CoV-2 Testing During the Pandemic

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is the causative agent of Coronavirus disease 2019 (COVID-19) [1]. This virus, from its humble beginnings in Wuhan, China, has since spread throughout the globe to become an international pandemic [2,3]. The impact of this pandemic has led to both critical supply shortages and an urgent need for tests and interventions before the usual full regulatory review by the Food and Drug Administration (FDA) [2,4 and 5]. These supply shortages have impacted the supply of critical materials and reagents for testing, such as personal protective equipment, viral transport media, swabs, and test reagents [4-6]. Concomitant with the supply shortages, that can truly hamper even the collection of specimens, is the issue that the pandemic can also lead to staffing shortages because staff members who are infected or exposed may need to quarantine [2,3]. The urgency in the need for tests has led the FDA to issue emergency use authorizations (EUA) for SARS-CoV-2 test assays [7]. The exclusive presence of only several EUA assays for SARS-CoV-2 testing represents a unique situation for the laboratorian as this pandemic is likely to be both the first and only time that a test with a EUA is run in his/her career. Effectively, the pandemic has created a new frontier of many tests under a EUA instead of having any test under full regulatory FDA approval [2].

This situation induced by the pandemic, with both supply and the uniqueness of only multiple EUA testing platforms, would apply to laboratories throughout the country, regardless of the population or region served. The experience and perspective from this pandemic would serve as a useful reference not only during the current pandemic but also for the future should a similar public health emergency reoccur. Therefore, we seek to summarize this laboratory perspective in a manner that could be referred to by any laboratory in the United States.

Challenges and Visualization of the Situation by the 6-stop Paradigm

A critical overall visualization of the situation for the laboratory preparing to implement SARS-CoV-2 testing can be summarized in a 6-stop paradigm that never actually ends if testing is in place (Figure 1). The responsible pathologist or laboratory director of any laboratory, regardless of the setting or population that it serves, is going to have to evaluate the many different available SARS-CoV-2 testing platforms available [2,3,7 and 8]. In evaluating these testing platforms, the responsible pathologist or laboratory director would need to compare the clinical needs of his or her facility with the testing characteristics (including but not limited to aspects such as sensitivity, specificity, availability of testing supplies, resource costs, and ease of testing) of the testing platforms [2,3]. Only after a thorough review and comparison with the clinical needs can a thoughtful decision on which testing platform the laboratory should implement can be reached.

In this review, the responsible pathologist or laboratory director needs to answer the question of why the test is being brought in and why that test assay for SARS-CoV-2. In this fashion, the laboratory director or responsible pathologist plays a critical role in collaboration with the clinical teams in selecting the assay. But the process does not end with merely selecting the assay. Even after assay selection, the laboratory and the clinical teams that it serves would need to contend with the supply situation and potential staff shortages [4,5]. Therefore a critical step for the laboratory (stop 2 in the paradigm) is verifying that it has enough supplies and the staff resources to perform the test to clinical expectations. Critical shortages of viral transport medium and swabs to collect the specimen or a need to ration test reagents or cartridges are issues that have not only been experienced by the authors but also experienced in laboratories throughout the nation [2,6]. Even early in the COVID-19 pandemic, it had become clear that gone were the days of being able to order everything and anything that could be needed for clinical and laboratory care [2,6]. Even critical reagents would routinely be on backorder from multiple or all available commercial vendors as the supply chain had been effectively snapped by the

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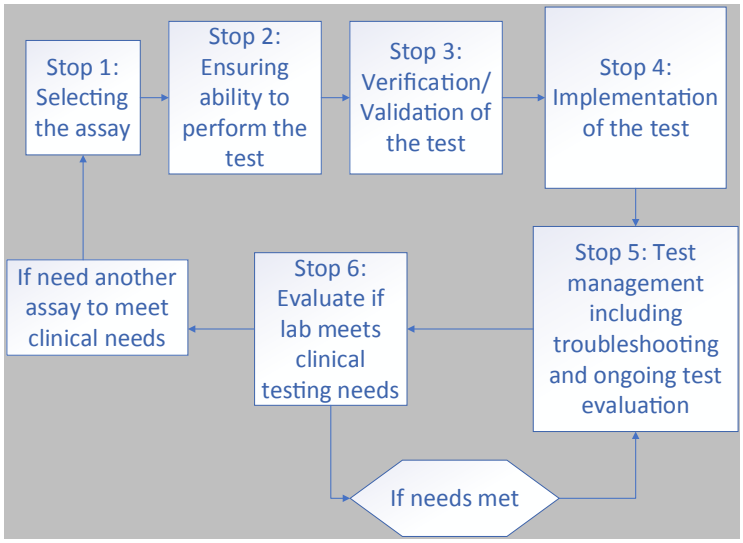

Figure 1: A critical 6-stop paradigm in SARS-CoV-2 Test implementation and management. Validating and implementing a test is only the beginning as once the test is implemented, there is a need for ongoing test evaluation and troubleshooting along with a need to evaluate if additional test assays may need to be introduced.

pandemic. Measures to improve or ration the supply may need to be undertaken if proactive procurement of supplies from available commercial vendors is not sufficient [5,6].

The 3rd stop is to properly verify or validate the test before putting the test into clinical use [8]. The process of verification and validation of laboratory tests is part of the minimal laboratory standards in the United States set by the Clinical Laboratory Improvement Amendment (CLIA). This step is effectively ensuring that the test works. The process of verification or validation of the test assay would include initial evaluation to verify the accuracy, precision, reportable range, and reference intervals [8]. Particularly for tests that are modified or laboratory-developed tests, additional aspects of the verification or validation would include analytical sensitivity (or determining the limits of detection), analytical specificity, and any other characteristic that the laboratory determines is needed for test performance. Although the manufacturer of the test assay may have already made claims for these parameters, it is still critical for the laboratory to verify or validate these claims.

This stop to properly verify or validate a test would be required for both points of care as well as assays run in the laboratory. Essentially, it must be confirmed that when the standard operating procedure is followed for performing the test by laboratory personnel, that the test performs as expected and can therefore be placed into clinical use.

After the responsible pathologist or laboratory director has determined that the test works, there are still steps in implementing the test in stop 4 [2,3]. Part of implementation includes educating and notifying the clinical teams about the test. This would include ensuring that clinicians can order the test as clinically indicated, that there exists a process for both specimen collection and delivery to the laboratory, that the laboratory information system allows accessioning and resulting of test results into the patient's medical record, and that there is appropriate post-test communication of results to the appropriate clinicians. The responsible pathologist or laboratory director plays a critical role in ensuring that the test is appropriately implemented to serve the needs of the clinicians.

Even after test implementation, there continues to be an ongoing need (stop 5) by the laboratory to manage the testing process [2]. Errors, which may vary depending on the test platform brought in by the particular laboratory, inevitably occur and require the laboratory's attention to troubleshoot and resolve the issues for quality patient care. Even in the absence of test analysis or post-analysis reporting issues requiring resolution, all test assays are susceptible to pre-analytic issues such as specimens collected in a compromised state. In addition, the supply situation for the test performance can change – as it did during the pandemic – making past relatively abundant supplies suddenly scarce; this changing situation would require management of the test for the most appropriate usage. All these potential matters requiring troubleshooting or management produce a constant and continuous critical role for the responsible pathologist or laboratory director.

At some point, the responsible pathologist or laboratory director needs to evaluate if clinical testing needs are being fully met by the currently available laboratory tests in stop 6 [2]. It may very well be that more than one test assay is needed to fully meet clinical needs. Test assays after all vary in terms of workflow, turnaround time, ease of testing, and access to supplies. For instance, the author's institution had implemented not only the Abbott m2000 and Abbott Alinity-m SARS-CoV-2 testing platforms (Abbott Park IL) for high laboratory specimen throughput, but also the SARS-CoV-2 testing on the Cepheid Infinity platform (Sunnyvale, CA), BinaxNOW point of care testing (Abbott Park IL), and the Ortho VITROS SARS-CoV-2 antigen test (Rariton NJ) to fulfil clinical needs. Specifically, these clinical needs ranged from the need for fast turnaround times for certain critical patient cases, access to a point of care test in the treatment room, to ease of testing given supply and staff constraints.

Ultimately, stops 5 and 6 never truly end if testing is in progress. The test assay must be troubleshot as issues arise and managed appropriately given changing circumstances, and this must continue even if clinical needs are being met. On the other hand, the clinical need for a test with different characteristics may restart the process in a full circle with a new SARS-CoV-2 assay to be brought into the clinical laboratory for clinical usage.

Conclusion

The SARS-CoV-2 pandemic created a unique situation that consisted not only of supply and staff shortages, but also a distinctive field of several test assays under EUA instead of the usual full regulatory approval. The characteristics of the pandemic that led to these issues include the impact the pandemic had on the supply chains of the economy and to the urgency for the nation to make tests available on a most urgent basis. In such a unique circumstance, the laboratory plays a critical and important role in the selection, validation/verification, implementation, management with troubleshooting, and evaluation of lab tests, all of which remain essential key components both within and outside of the pandemic, in normal times and times of emergency, and even if another similar public health emergency occurs in the distant future.

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