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COMMENTARY

Understanding, Verifying, and Implementing Emergency Use Authorization Molecular Diagnostics for the Detection of SARS-CoV-2 RNA

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ABSTRACT The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has brought a new wave of challenges to health care, particularly in the area of rapid diagnostic test development and implementation. The diagnosis of acute coronavirus disease 2019 (COVID-19) is critically dependent on the detection of SARS-CoV-2 RNA from clinical specimens (e.g., nasopharyngeal swabs). While laboratory-developed testing for SARS-CoV-2 is an essential component of diagnostic testing for this virus, the majority of clinical microbiology laboratories are dependent on commercially available SARS-CoV-2 molecular assays. In contrast to assays approved or cleared by the U.S. Food and Drug Administration (FDA) for *in vitro* diagnostic use, assays for the detection of SARS-CoV-2 nucleic acids have emergency use authorization (EUA) from the FDA. Outside of highly specialized academic and commercial laboratory settings, clinical microbiology laboratories are likely unfamiliar with the EUA classification, and thus, assay verification can be daunting. Further compounding anxiety for laboratories are major issues with the supply chain that are dramatically affecting the availability of test reagents and requiring laboratories to implement multiple commercial EUA tests. Here, we describe guidance for the verification of assays with EUA for the detection of SARS-CoV-2 nucleic acid from clinical specimens.

KEYWORDS COVID-19, EUA, verification, coronavirus, validation

The coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated respiratory tract illness has created an unprecedented demand for diagnostic testing. Infection with SARS-CoV-2 leads to a range of outcomes, from asymptomatic infection to mild and moderate symptoms, including fever and cough, to the requirement of intensive respiratory support and death. According to the Johns Hopkins University COVID-19 Dashboard, as of 6 May 2020, there have been over 3.7 million confirmed cases of COVID-19 and more than 258,000 deaths worldwide, with the United States representing the country with the largest number of reported cases and deaths to date. Unfortunately, many cases are likely to have gone undocumented because testing resources have been limited, such that testing has been predominantly restricted to the most-at-risk individuals. As more resources are produced and more testing is implemented, less acute cases of COVID-19 should be able to be tested and identified.

The slow implementation of testing and the lack of testing capacity have repeatedly

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made headlines. Initial problems with the CDC test led to the delayed deployment of testing to public health labs and restricted testing to the CDC for several weeks. Further delaying the implementation of testing was the requirement for laboratory-developed tests (LDTs) to be submitted for U.S. Food and Drug Administration (FDA) emergency use authorization (EUA) review (discussed below) and shortages of collection devices, extraction kits, master mix, and other commercial reagents. Additionally, commercial manufacturers of diagnostic devices took several additional weeks to develop and submit assays to the FDA for EUA review and were unable to meet supply demands for reagents or instruments once tests were approved. Not only was the demand for test components greatly increased worldwide, but also the manufacturing facilities for many products were located in parts of the world that were the hardest hit by the pandemic. The combination of widespread lockdowns impacting transportation and production and the excess expenditure associated with COVID-19 medical responses has led to a downturn of the global economy and a broken supply chain (1). Additional laboratory challenges to implementing molecular testing for SARS-CoV-2 include a lack of positive-control materials, personnel/time, primers/probes, a specificity panel, funds, a quality control (QC) system, commercial tests, procurement procedures, training, and equipment (2).

The continued need to increase testing capacity is based on the desire to test both asymptomatic and symptomatic individuals, particularly as countries begin to restart their economies. Detection of SARS-CoV-2 RNA from respiratory tract samples is an important component of outbreak management. The rapid and accurate identification of infected individuals, whether they are symptomatic or asymptomatic, is critical to enforce self-isolation recommendations, contact tracing in the community, and the use of appropriate enhanced personal protective equipment (PPE) in health care settings. Positive SARS-CoV-2 RNA detection is also important for therapeutic clinical trials. Negative results obtained from highly sensitive tests on inpatients with symptoms of COVID-19 can help prevent the overuse of enhanced PPE by medical providers. Similarly, negative results obtained for health care personnel can assist in maintaining adequate levels of staffing. It is important to note that the reliability of negative test results can be confounded by the stage of disease, the adequacy of sampling, the performance characteristics of the test, and disease prevalence.

Laboratory-developed nucleic acid amplification tests have been a mainstay for academic medical centers and commercial laboratories for decades. They have been particularly helpful in rapidly deploying diagnostics for new or emerging infectious diseases, like SARS-CoV-1, Middle East respiratory syndrome coronavirus (MERS CoV), the 2009 pandemic influenza A(H1N1) virus [influenza A(H1N1)pdm09 virus], and enterovirus D68 (3). Usually, laboratories can develop and validate LDTs under the Clinical Laboratory Improvement Amendments (CLIA) regulation without direct oversight by the FDA. However, when a public health emergency (PHE) is declared for a new infectious disease of public health importance, laboratories cannot offer LDTs for the PHE agent without applying for and being granted EUA by FDA. The concept behind the FDA's EUA process is to strengthen public health protections and facilitate the availability and use of medical countermeasures (MCMs), such as drugs, vaccines, medical equipment and supplies, and diagnostics (4). The goal is to make MCMs readily accessible during a public health emergency while still protecting the public, by providing an authorization process less stringent and more streamlined than that usually required for full FDA approval.

On 4 February 2020, the secretary of health and human services declared the potential for a PHE from COVID-19 and EUA authority for associated MCMs, including diagnostics. Any laboratory or commercial company developing molecular tests for the detection of SARS-CoV-2 had to submit an application to FDA and obtain EUA status in order to offer the test for diagnostic purposes. Most laboratories lacked experience with the EUA process and found the prospect daunting because most had experience only with clinical trials leading to *in vitro* diagnostic (IVD) submissions to FDA, which are quite complex. The prospect of overseeing such a process while directing a laboratory

in the midst of a pandemic was intimidating, causing many LDTs to remain unused and unimplemented. On 29 February 2020, the FDA issued new guidance and streamlined the EUA process for CLIA-certified laboratories that allowed clinical testing to begin, as long as the abbreviated EUA application was submitted within 15 days. Several laboratories began offering their LDTs through the streamlined EUA process, though FDA review was still required. On 16 March 2020, the guidance was further updated, giving states the option of overseeing the validation process for CLIA-certified laboratories. States that have notified FDA that they will take responsibility for COVID-19 testing in their state as of 6 May 2020 are Connecticut, Maryland, Mississippi, Nevada, New Jersey, New York, and Washington. An important addition to the 16 March guidance was the ability of commercial manufacturers to distribute their test kits after validation as research use only while the EUA submission was being prepared and under review. This led to a rapid increase in the number of commercially available EUA tests for the detection of SARS-CoV-2 RNA for clinical testing, which was a critical step toward increasing testing capacity in the United States. However, despite the addition of numerous commercial tests with EUA, a testing gap remains due to chronic shortages of testing reagents, materials, and instruments, as well as specimen collection swabs and transport media.

The EUA process does not include classifying tests into traditional categories, such as CLIA waived or FDA cleared, and EUA is a temporary designation that is usually discontinued once the PHE is declared over. It should be noted that the studies performed by laboratories and manufacturers to define the performance characteristics for EUA tests are less stringent than those required of an IVD test. Studies for EUA submission primarily focus on analytic sensitivity (i.e., limit of detection) and analytic specificity (i.e., cross-reacting organisms). Under EUA, clinical trials to establish clinical sensitivity and specificity are not required due to the novelty of the pathogen and the absence of both reference methods and a clearly defined disease state. As of May 2020, the clinical sensitivity of assays that have received FDA EUA have not been determined by extensive study. However, as for most diseases, there are reports of individuals with COVID-19 who have negative SARS-CoV-2 RNA test results, and thus, a negative nucleic acid test result does not definitively rule out COVID-19 (5).

Commercial EUA tests are not FDA-cleared/approved tests, nor are they considered laboratory-developed tests, so there can be confusion regarding how to verify these tests. Verification of commercial EUA tests should include assessment of accuracy and precision in a fashion similar to that for IVD assays, as long as there is no modification to the test, as described under the EUA. Furthermore, attention should be paid when considering an EUA assay on a device that is typically considered to be for use at the point of care (POC). It is recommended that the FDA letter of authorization be reviewed to determine if the EUA allows for testing in a true POC setting (e.g., physician office, usually run by nonlaboratory staff) or requires the testing to be conducted within a lab certified to perform moderate- or high-complexity testing. These letters of authorization can currently be found at the FDA website (6). It is important to keep in mind that while the instrument may be for POC use, the assay itself is not, and the test, even if it is performed on a POC device, requires a verification prior to being used. Many current CLIA-waived assays do not require a verification prior to clinical testing, so the concept of verification to establish test performance may be a new concept to those running the test. Clinical microbiology laboratories may consider assisting POC testing departments with the verification process to ensure that the EUA test performs as expected.

Of the commercial molecular SARS-CoV-2 assays receiving EUA status, there are direct sample-to-answer, POC devices, as well as those designed for high-complexity batched-based testing. Some commercial molecular assays offer rapid detection of a viral pathogen directly from patient specimens (7). However, it is important to consider the limitations of these assays that are included in the instructions for use document (i.e., package insert) provided by the manufacturer. These limitations may include the acceptable specimen types, specific extraction and amplification procedures, the avail-

ability of trained staff, and the laboratories where tests can be performed (6). Because of variations among tests between different vendors with respect to approved sample types, collection/transport media, swabs, and test performance, review of the FDA authorization letter is recommended before deciding to implement a test. A bridging study or independent EUA submission to the FDA may be required if a laboratory modifies a commercial EUA test from its instructions for use in any way. Bridging studies and the processes for developing a laboratory-developed test for EUA submission will not be discussed here. Guidance on how to perform these studies can be reviewed on the FDA website (8). Readers are directed to contact the FDA at covid19dx@fda.hhs.gov with additional questions regarding these. Here, we provide guidance for the verification of nonmodified commercial EUA tests for the detection of SARS-CoV-2 RNA.

BIOSAFETY

Commercial EUA test verification requires the use of appropriate biosafety and protective equipment while handling, manipulating, and testing specimens. An internal risk assessment of the device and its potential use in the user's location, particularly POC devices, should be done to ensure that proper biosafety and PPE are employed. Risk identification and mitigation are critical in maintaining a safe laboratory environment. Therefore, risk assessment plans should be in place to identify and mitigate the risks associated with SARS-CoV-2 diagnostic testing procedures. A plan to mitigate risks should be documented after prioritizing the risks and should be communicated to the laboratory personnel performing the tests. Risk assessment and mitigation strategies are dependent on the procedures performed, the identification of hazards associated with the procedures, the competency level of the laboratory staff, the laboratory equipment and facility, and the available resources (9).

Good laboratory practices should be followed at all stages of SARS-CoV-2 diagnostic molecular testing. Appropriate disinfectants should be used for decontamination of work surfaces and equipment (9, 10). For laboratory-based testing, a certified class II biological safety cabinet (BSC) should be used for procedures with the potential to generate aerosols and droplets. In locations without a BSC, additional precautions should be implemented to reduce the risk of exposure, which may include the use of additional PPE, such as a surgical mask and a face shield or splash shield. Specimens may be heat inactivated (56°C for 30 min), but a bridging study is required if this is not specified in the instructions for use. A biohazard risk assessment plan should be in place to identify any additional risks and precautions. All laboratory waste generated from the testing of confirmed or suspected SARS-CoV-2 patient specimens should be considered biohazardous waste and handled in a manner similar to that used for biohazard waste.

GENERAL CONSIDERATIONS FOR VERIFICATION

Acceptable specimens should be collected in the transport media recommended by the FDA or manufacturer (11). Samples used for the verification should be the same as or similar to samples that will be used for clinical testing. The primary materials required to conduct a verification procedure include, at a minimum, 10 positive and 10 negative specimens, commercially available reference material (e.g., Accuplex, Exact, NAtrol) or residual patient samples, and SARS-CoV-2 reagents authorized by the FDA EUA. The instruments used for testing should be based on those specified in the FDA EUA authorization documents for the commercial tests (6). Verification is a two-step process. The first is performance of the manufacturer's described quality control (QC) instructions to verify that controls have produced the expected results. The second includes accuracy and precision studies and should proceed after successful completion of the QC verification.

QUALITY CONTROL

QC is a step critical to any verification procedure to ensure that cartridges, reagents, and the instrument are working properly. The manufacturer should be contacted if QC

is not successful. QC material is also required for developing an individual quality control plan (IQCP). The material can be synthetic commercial products, residual patient samples, or genomic or *in vitro*-transcribed RNA. However, genomic or *in vitro*-transcribed RNA is generally not recommended on account of stability issues. The use of quantified, inactivated virus QC material is preferred over the use of nonquantified material or RNA and should contain every SARS-CoV-2 target detected by the assay. If QC material is included in the commercial EUA test kit, it should be used per the manufacturer's instructions. Otherwise, when it is not included with the test kit or if the QC included does not include the SARS-CoV-2 target(s) (e.g., a processing control only), it must be purchased independently. Recommendations on the use of external quality control material can be obtained from the EUA test manufacturer. In the absence of commercial QC material, residual patient samples can be used for external quality control. A large batch of positive controls (a 1:10-diluted, a heat-inactivated, or a moderate positive patient sample) should be made, aliquoted for single use, and stored at −80°C. Residual negative patient samples should be used as a negative control. The use of purified genomic viral RNA may also be an option for QC purposes. However, its use is more challenging than the use of intact virus, as RNA is fragile and degrades more readily than intact virus. This requires special handling and storage conditions that may present challenges for laboratories unaccustomed to working with RNA. The recombinant or *in vitro*-transcribed RNA, when used, should match the target gene(s) of the assay. A large batch of the positive control should be made by spiking the quantified RNA into a prelysed negative sample matrix (moderate positive, 5,000 genome copies/ml), aliquoted for single use, and stored at −80°C. Spiking of RNA into lysed samples is suggested to prevent RNA degradation. Of note, viral RNA is not recommended as QC material in verification samples for cartridge-based assays because RNA degradation begins as soon as patient samples are spiked directly with RNA. External QC must be run every day of patient testing or according to the manufacturer's instructions. An IQCP can be developed for EUA tests with an internal control that could serve as the daily control. CLIA requirements should be followed for implementing and monitoring the IQCP (12). While the number of days of continuous QC that is required for IQCP is up to the laboratory medical director to determine, a minimum of 20 days is commonly practiced and generally considered acceptable.

ACCURACY

The verification procedure should be similar in approach for both batched and nonbatched (i.e., random access, sample to answer) assays (13). During accuracy and precision studies, it is recommended that carryover contamination be assessed by alternating positive and negative specimens during verification for both batched and nonbatched assays. Limit-of-detection (LOD) verification is not required for the on-label use of EUA assays. Verification of accuracy can be performed using two options: (i) contrived patient samples (option 1) or (ii) remnant patient samples tested for SARS-CoV-2 RNA by another EUA test (option 2).

In option 1, contrived patient samples are created by spiking pooled negative matrix (i.e., pooled residual negative patient samples) with commercial materials, ideally quantified by the manufacturer. Blank transport medium can be used as a pooled negative matrix if residual negative patient samples are not available. It is important to note that in transport media, the internal control will be negative if it targets a human gene (e.g., RNase P). Positive reference material can be run neat or diluted 1:2 or 1:10 to represent a strong positive sample or a moderate positive sample, respectively. It is recommended that users contact the manufacturer or refer to the manufacturer's instructions to determine if the product can be diluted with transfer medium or must be diluted with the commercial synthetic negative matrix. Testing should include a minimum of 10 positive samples, including 5 strong positive and 5 moderate positive samples, which can also be used for precision studies (see below). In addition, at least 10 negative remnant patient specimens should be tested. If patient specimens are not available or are limited, contrived negative samples can be created by pooling fewer

TABLE 1 Dilutions based on C_T values

Sample no.	Reference method C_T value (neat)	Expected C_T value at a dilution of[a]:						
		1:10	1:100	1:1,000	1:10,000	1:100,000	1:1,000,000	1:10,000,000
1	15	18	21	24	27	30	~~33~~	~~36~~
2	25	28	31	~~34~~	~~37~~	~~40~~	~~43~~	~~46~~
3	30	~~33~~	~~36~~	~~39~~	~~42~~	~~45~~	~~48~~	~~51~~

[a]Shaded strikethrough values may approach the LOD of the assay and should not be used in verification studies.

specimens and testing 10 times. If discordant results are obtained, the specimen should first be retested by the test under verification. If the discordance is resolved, additional training and/or additional specimens may need to be tested to complete the verification. If the discordance is not resolved, consider testing the specimen by an alternative method or contact the manufacturer for additional guidance.

In option 2, residual patient samples tested by another EUA method can be used for verification. While most PCR-based EUA methods provide a PCR cycle threshold (C_T) value, some instruments may not allow such data to be accessed, and therefore, the strength or weakness of the sample cannot be assessed. Additionally, laboratories that initially used reference labs for testing may not have C_T values available for reference. In this instance, when saving samples for verification of a commercial EUA test, it is recommended to reach out to the respective reference lab to gather the C_T values for the few positive samples that will be used for verification purposes. Testing should be performed on 10 positive residual samples (independent patient samples that are not pooled or dilutions of a strong positive sample) and 10 negative residual samples (independent patient samples that are not pooled). If 10 independent positive specimens are not available, a strong positive sample can be diluted to obtain 5 strong positive samples and 5 moderate positive samples. The identification of a strong positive sample is based on the PCR threshold value: C_T values range from 15 to 24 for strong positive samples and 25 to 30 for moderate positive samples. Tenfold serial dilutions of positive specimens can be made in remnant pooled negative residual patient samples or transport media to achieve the desired C_T value. The LOD is an important parameter to consider when making dilutions to ensure that dilutions do not reach or go past the LOD of the assay. Every 10-fold dilution will increase the C_T value by approximately 3 cycles (Table 1). For example, a 10-fold dilution of a sample with an initial C_T value of 20 will result in a C_T value of approximately 23. It is critical to note that an initial C_T value of >31 may approach the LOD after delayed transport or multiple freeze-thaw cycles. It is recommended that such samples not be included in accuracy studies.

PRECISION

The general recommendation for precision studies is to test one strong positive sample, one moderate positive sample, and one negative sample, each in triplicate. The negative sample can be either an individual negative sample or pooled negative samples, based on available resources. It is recommended that precision be performed by different operators either over different shifts or on different days. While interprecision (reproducibility) and intraprecision (repeatability) are recommended for high-complexity testing, intraprecision does not apply for cartridge-based assays in which each cartridge is independent of the other cartridges. It is recommended that interprecision be determined for all commercial EUA assays, regardless of the test format. However, for commercial EUA assays that are in a batched format (e.g., 96-well plate), intraprecision should also be assessed in a manner similar to that used for interprecision. The precision studies can be performed by comparing the C_T values of the same positive samples run in triplicate.

ADDITIONAL CONSIDERATIONS

For laboratories that are a part of a large health care system or reference laboratories that aim to implement the same cartridge-based or POC EUA assay throughout the

TABLE 2 Suggested comments for reporting SARS-CoV-2 EUA results

Result or comment type	Comment
Negative for SARS-CoV-2 RNA	This assay is designed to detect the XXXX and/or XXXX gene of SARS-CoV-2 using nucleic acid amplification. A [not detected or negative] result does not preclude the possibility of SARS-CoV-2 infection since the adequacy of sample collection and/or low viral burden may result in the presence of viral nucleic acids below the analytical sensitivity of this test method. Test results should be used with other clinical and laboratory data in making the diagnosis.
Universal comment	This test has received FDA emergency use authorization and has been verified by the XXXX laboratory. This test is authorized only for the duration of the public health emergency declaration and the circumstances that exist to justify the authorization of the emergency use of *in vitro* diagnostic tests for the detection of SARS-CoV-2 and/or diagnosis of COVID-19 under section 564(b)(1) of the Act, 21 U.S.C. 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.
Universal comment	This testing was performed in the XXXX laboratory, located at [Anywhere, USA 12345] (CLIA certificate number XXXXXXXX, accreditation number XXXXXXXX, other as appropriate).

system, in efforts to conserve testing supplies while still ensuring that the assay performs as expected, a full verification (as described above) may be performed at the main or core laboratory before any clinical testing begins. If the full verification meets expectations, then a verification using a smaller panel with 6 positive specimens and 4 negative specimens can be performed at each affiliated site within the system using the same instrumentation. Of the 6 positive samples, 3 should be strong positive and 3 should be moderate to low positive, as described above. One positive patient sample tested in triplicate or replicates of QC material can be used for precision. Negative samples should be negative residual patient samples used for accuracy. The main laboratory can develop and distribute miniverification panels to aid the process. The steps for the miniverification at each site are similar to those for the main verification, where QC is performed and deemed acceptable before proceeding with additional testing. Each individual site should use the miniverification panel to verify its device, which can also be used as part of the technical staff training. Before taking this approach, each lab or system should consider the degree of medical oversight, staffing, work flow, availability of biosafety equipment, and appropriate quality assurance procedures at each remote laboratory. Note that this approach is not recommended for either high-complexity EUA tests or laboratory-developed tests. Staff training and competency should be documented appropriately as for all other assays in the clinical laboratory. If required by the health system, results should be submitted to the main/central laboratory for review and approval. The full verification summary from the main laboratory should be made available to satellite labs in case it is requested or required by regulatory agencies. QC should be run at each site per the manufacturer's instructions. If an IQCP is an option, each site must perform its own risk assessment before developing and implementing an IQCP.

If a laboratory intends to implement a multiplexed pathogen panel to which SARS-CoV-2 has been added, the verification approach may vary depending on how the new target is incorporated into the panel. If it has been added as a separate reaction, the verification can be performed on the SARS-CoV-2 target alone, as described above. If it is incorporated as a multiplexed assay with any of the other target assays in the panel, the new target (SARS-CoV-2) must be verified as described above, and additionally, the performance of the assay for the other targets that it is multiplexed with must be verified by running low-level-positive controls for those targets and demonstrating no loss of detection by the addition of the SARS-CoV-2 assay.

REPORTING

After the assay has been verified and clinical testing begins, there are considerations regarding how the results should be reported. Table 2 lists comment examples that could be customized and added to all test reports. Other resources are available to clinical labs verifying and performing EUA SARS-CoV-2 diagnostics. FDA requires fact sheets to be shared with providers and patients. These should be included in all test reports or physically distributed to the individuals. Fact sheets can currently

be found here: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd. COVID-19 is currently a reportable disease; a system should therefore be in place to properly notify the appropriate public health agencies of cases in which SARS-CoV-2 RNA is detected.

The rapid emergence and spread of SARS-CoV-2 have posed unprecedented challenges for assay development and deployment; regulatory oversight systems; reagent, material, and instrument resource allocation; the validation, verification, and implementation of testing services; and the response to major surge testing loads. The cooperation of partners and stakeholders across clinical, public health, and commercial laboratories, as well as industry and regulatory authorities, has been critical in order to navigate the myriad of issues with the necessary speed and scope of changes that have occurred. Clarification, further discussions, and resolution will continue in the coming months and future years as we continue to learn from the events of the SARS-CoV-2 pandemic.

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