Implementing a SARS-CoV-2 Test in Your Laboratory

In the rapidly evolving landscape for diagnostic testing for the SARS-CoV-2 virus, the CAP can help clarify and simplify the rules of compliance so that you can efficiently and safely introduce testing in your laboratory to serve your patients during this public health emergency.

COVID-19 Diagnostic Tests

You can use the links below to see a current list of COVID-19 tests approved via the US FDA's Emergency Use Authorization and the WHO's Emergency Use Listing:

United States:

https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covidinvitrodev

Laboratories subject to US regulations, may only use:

- Tests authorized through the FDA's EUA process
- Tests developed by the laboratory
- Tests authorized by the state where the laboratory is located

Validated tests that will be submitted to the FDA for EUA may be distributed and used prior to obtaining EUA under the conditions define by the FDA. Review the FDA policy for more information.

Worldwide:

https://www.who.int/diagnostics_laboratory/EUL/en/

International laboratories (not subject to US regulations) may use the following types of tests, if allowed by country and regional regulations and guidelines:

- Tests authorized through the FDA's EUA process
- Tests listed on the World Health Organization Emergency Use Listing (EUL)
- Tests approved by internationally recognized regulatory authorities (eg, CE-Marking)
- Tests developed by the laboratory

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Verification Requirements for FDA Emergency Use Authorized (EUA) Tests

For unmodified FDA EUA tests obtained from an authorized manufacturer, laboratories must verify the test method performance specifications as applicable to the test's designated authorized setting. All tests must be approved for use by the laboratory director or designee meeting CAP director qualifications prior to beginning patient testing.

For tests authorized for use in a patient care setting—follow manufacturer's instructions for waived test implementation (COM.30980) at minimum. The FDA deems these tests to be CLIA waived, even if testing is performed in the main laboratory under a CLIA certificate of accreditation or registration.

For tests authorized for use in moderate or high complexity testing laboratories only—verify analytical accuracy, precision, reportable range, and reference intervals.

Applicable checklist requirements for nonwaived testing include:

COM.40300	Verification of Test Performance Specifications - FDA-cleared/approved Tests
COM.40475	Method Validation and Verification Approval - Nonwaived Tests
COM.40500	Analytical Interferences

While the ultimate objective is to fully verify the method performance of the assay, the urgent need for patient testing and shortages of reagents and supplies during the health care crisis makes it difficult to fully evaluate the accuracy, precision, and reportable range as stated in COM.40300. A more limited approach may be acceptable. You and your laboratory director should determine the depth of verification needed to begin testing. Your laboratory director must approve the method verification prior to testing (COM.40475).

Some commercial test kits may have QC materials for checking performance of the test kit. For accuracy verification (COM.40300), laboratories may use known positive and negative patient specimens, positive and negative QC materials, and other commercially purchased materials. The use of contrived (spiked) patient specimens is no longer recommended for test method verification due to the increased availability of positive natural clinical patient specimens. The CAP encourages laboratories to continue to evaluate assay performance with actual patient specimens.

For analytic interferences (COM.40500), the kit manufacturer or CDC may be able to provide a list of interfering substances.

Download a template for analytical verification by searching "analytic verification" at cap.org (login required).

Laboratories that develop their own assays are required to perform a complete validation study (refer to the section below on Laboratory-Developed Tests).

International Laboratories Test Verification Options

The instructions above for test method verification also apply to laboratories not subject to US regulations that are using FDA EUA assays. In addition, it applies to:

- Tests listed on the WHO EUL
- Tests approved by internationally recognized regulatory authorities (eg, CE-Marking)

Laboratories that develop their own assays or obtain test kits through unapproved or unauthorized sources are required to perform a complete validation study (refer to the section below on Laboratory-Developed Tests).

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Modifications to Approved/Authorized Test Kits

There have been shortages of certain types of supplies and equipment needed for specimen collection and testing (eg, transport medium, swabs) for COVID-19 EUA assays. The FDA provides recommendations in its frequently asked questions for alternative products that may be used based on the best available evidence and in consultation with outside experts. The FDA recommendations are updated as the FDA receives more information from laboratories and manufacturers on other validated alternatives.

Laboratories may also validate other alternatives. This can be accomplished through the use of a bridging study where the new component is evaluated for equivalent performance using parallel testing of the same specimens with new and original components.

Validation Requirements for Laboratory-Developed Tests

Laboratories developing tests for COVID-19 must establish accuracy, precision, reportable range, reference intervals, analytical sensitivity, and analytical specificity (interferences), as applicable. The tests must be validated at the laboratory performing the test.

Applicable checklist requirements include:

COM.40350	Validation of Test Performance Specifications - Modified FDA-cleared/approved and LDTs
COM.40475	Method Validation and Verification Approval - Nonwaived Tests
COM.40500	Analytical Interferences
COM.40830	Test List - Modified FDA-cleared/approved and LDTs
COM.40840	Calibration and Quality Control Procedures - Modified FDA-cleared/ approved and LDTs
COM.40640	Clinical Claims Validation
COM.40850	LDT and Class I ASR Reporting

Download a template for analytical validation by searching "analytic validation" at cap.org (login required).

Review FDA templates for EUA submission for guidance on aspects to be considered during test development or if you are considering distribution of the test system to other laboratories.

Personnel Qualifications for COVID-19 Testing

Review the personnel qualifications defined in the Laboratory General Checklist (GEN.54750) to identify the qualifications needed to perform testing in your laboratory.

The applicable personnel requirements are based on the complexity of the test performed.

- Tests authorized under the FDA's EUA process—The Letter of Authorization for each EUA assay defines the setting in which the test may be used. Many are authorized for use in moderate and high complexity laboratories. If a test is also authorized for use in a point-of-care setting, it is deemed to be CLIA waived.
- All other types of testing are considered high complexity testing. This includes:
    - Tests with FDA notification, pending EUA
    - State-authorized assays
    - Laboratory-developed tests

The complexity of tests with EUA can be found on the FDA website

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Quality Control or IQCP for COVID-19 tests?

The following is the CAP's current guidance for performing quality control for COVID-19 testing **during the COVID-19 health care crisis:**

- For EUA tests **authorized for use in a patient care setting**, perform quality control following the manufacturer's instructions, at minimum. The FDA deems these tests to be CLIA waived tests. No IQCP is required.
- For EUA tests **authorized for use by moderate or high complexity laboratories only**, perform quality control following the manufacturer's instructions, at minimum. These tests are nonwaived tests; however, no IQCP is required **unless** the manufacturer does not define conditions for reduced external QC frequency in its instructions for use and the laboratory wishes to perform QC less frequently than the CLIA default of two levels of QC each day of testing.

If the manufacturer does not define conditions for reduced external quality control in its instructions for use (eg, states to perform external QC in accordance with applicable federal, state, or local accreditation requirements), the laboratory must:

- Perform external QC following the default CLIA frequency (eg, two levels of QC each day of testing) **OR**
- Implement an IQCP to reduce the frequency of external QC. Written QC plans must be approved by the laboratory director prior to implementation.

Please note that all laboratories performing nonwaived testing must perform external QC with each new lot and shipment of reagents.

Visit the CAP's IQCP Toolbox for resources to develop an IQCP by logging into e-LAB Solutions Suite and searching for "IQCP Toolbox."

How Can we do Proficiency Testing?

The CAP has a comprehensive offering of proficiency testing (PT) and quality improvement programs to meet your laboratory needs for COVID-19 testing. Details about each program are included on cap.org.

- COV2—Detection of SARS-CoV-2 by nucleic acid amplification testing
    - Specimens are non-infectious and target gene regions N, E, RdRp, S, and ORF1a.
- COVS—Detection of total, IgG, IgM, and IgA antibodies to SARS-CoV-2
    - Specimens are non-infectious donor-based serum and are compatible with most testing platforms.
- COVAG—Detection of the antigen of the SARS-CoV-2 virus
    - Specimens contain inactivated SARS-CoV-2 virus.

The CAP also offers a comprehensive portfolio of **Quality Cross Check** programs to complement your laboratory's SARS-CoV-2 molecular (COV2Q), serology (COVSQ), and antigen (COVAQ) testing that can be used to monitor performance and assess comparability on multiple platforms at numerous locations.

You can order these programs today in the online store or by contacting the CAP at 800-323-4040. Laboratories in countries served by a designated CAP distributor should contact the distributor's customer service department to order these products. Laboratories should check with their local authorities to determine if permits are required. Supporting documentation is available from the CAP upon request.

Laboratories must perform alternative performance assessments to determine the reliability of analytic testing at least semiannually. It is the responsibility of the laboratory director to define alternative performance assessment procedures and criteria for successful performance in accordance with good clinical and scientific laboratory practice. Common alternative performance assessment procedures include participation in a split-sample analysis with another laboratory, split-sample analysis with an established in-house method, use of assayed materials, and other suitable and documented means.

Reference CAP accreditation checklist requirement COM.01500.

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How to Add a COVID-19 Test to the CAP Activity Menu?

Update your laboratory's activity menu in Organizational Profile by logging into e-LAB Solutions Suite on cap.org.

The following activities are being used to identify COVID-19 assays:

- **Molecular-based assays:**
  - nCOV 2019, NAA, EUA, non-waived
  - nCOV 2019, NAA, LDT
  - nCOV 2019, NAA, EUA, waived*
  - nCOV 2019, NAA, EUA, waived, POCT*

If molecular testing is performed by next generation sequencing (NGS), add the appropriate activity above and the specific NGS activities from the list below that apply to the portion of testing performed at your laboratory. Laboratories using NGS for COVID-19 testing are inspected with both the Molecular Pathology and Microbiology Checklists.

  - NGS, analytical wet bench, Molecular Pathology
  - NGS, bioinformatics, Molecular Pathology
  - NGS, interpretation, Molecular Pathology
  - NGS, Microbiology

- **Antigen assays:**
  - SARS (CoV) antigen, EUA, waived
  - SARS (CoV) antigen, EUA, waived, POCT
  - SARS (CoV-2) antigen, EUA non-rapid method
- **Serological assays:**
  - nCOV 2019 antibodies
  - nCOV 2019 antibodies, flow cytometry
  - nCOV 2019 antibodies, rapid test, POCT

***The waived activities** may only be used for assays that have received authorization by the FDA for use in the **patient care setting**. Assays that have only received authorization for CLIA-certified moderate and high complexity laboratories must use the non-waived activity, even if the test is performed in a patient care setting.

If you are unsure how your laboratory's test was authorized, review the EUA Letter of Authorization for your specific test on the FDA website.

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Which COVID-19 Results Need to be Reported to State or Local Public Health Authorities?

Laboratories subject to US regulations must report all **positive and negative tests** performed to detect SARS-CoV-2 or to diagnose a possible case of COVID-19 to state or local public health authorities. This includes:

- Molecular, antigen, and antibody tests performed by all methods
- Laboratories with all CLIA certificate types (Certificate of Accreditation, Compliance, Registration or Waiver, and Provider-Performed Microscopy), regardless of the location of testing.

There are new and modified CLIA regulations that address failure to report that include provisions for sanctions and civil money penalties for noncompliance with reporting. Read the CAP's eAlert notification to learn more about changes in the Laboratory General Checklist requirement GEN.41316 that are effective immediately for all laboratories subject to US regulations.

Laboratories that are not subject to US regulations need to follow national, federal, state (or provincial), or local requirements for reporting results to public health authorities.

Analytical Verification/Validation[1]

VERIFICATION:

- **P**recision
- **A**ccuracy
- **R**eportable Range
- **R**eference Interval

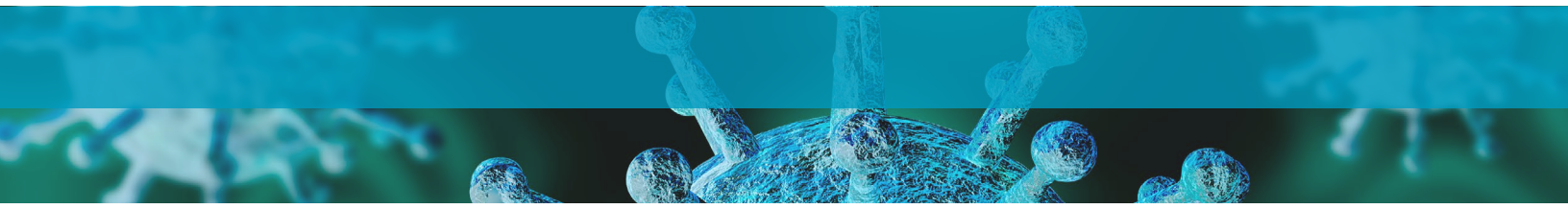
Mnemonic: PARR

VALIDATION:

- **P**recision
- **A**ccuracy
- **R**eportable Range
- **R**eference Interval(s)
- **A**nalytical Sensitivity (LOD)
- **A**nalytical Specificity (Interferences)
- Establish calibration and control procedures
- Other performance criteria

Mnemonic: PARR + AS + AS

1. Reference: Halling KC, Schrijver I, Persons DL. Test verification and validation for molecular diagnostic assays. *Arch Pathol Lab Med*. 2012;136:11-3



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