COLLEGE of AMERICAN PATHOLOGISTS

The College of American Pathologists: Clarifying Tests for COVID-19

The College of American Pathologists (CAP) is providing the following information to address the two types of tests, molecular and antibody, widely available for the novel (new) coronavirus SARS-CoV-2 and the disease it causes, coronavirus disease 2019 or COVID-19. A third type of test to detect SARS-CoV-2 antigen is beginning to come to market, but the clinical performance characteristics of these antigen tests have not been well studied, yet. We will continue to update the information in this rapidly changing testing environment in response to the COVID-19 pandemic.

	Molecular test: Detects active infections with SARS-CoV-2	**Antibody test: Detects the presence of antibodies against the SARS-CoV-2 virus**
Who should receive the test?	Molecular tests look for active infection with SARS-CoV-2 by detecting the presence of genetic material (RNA) specific for SARS-CoV-2. Decisions on whether a patient should be tested can be determined by a primary care physician, other health care provider, or public health authority based on current symptoms or exposure to the virus. The Centers for Disease Control and Prevention (CDC) guidelines remain focused on testing: symptomatic patients, first responders, and high-risk populations such as minorities, and those in nursing home facilities, prisons, and homeless shelters. Many health care organizations are recommending or requiring testing prior to elective procedures. Patients should consult with their primary care physician or other health care provider to understand results and any needed follow up.	In general, serology (or antibody) tests will reveal if a person has been exposed to the virus or infectious agent or vaccinated against the agent. In COVID-19 serology testing, antibodies can be produced if a person had an infection or if they were exposed to the SARS-CoV-2 virus. The serology test is not a diagnostic test and is not intended for the detection of an active infection. Patients should consult with their primary care physician or other health care provider to understand results and any needed follow up.
How is the specimen collected?	Molecular tests typically require upper respiratory samples with nasopharyngeal swabs being the most common. Lower	Serology tests require serum/plasma or a finger-stick blood sample.

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	respiratory secretions such as sputum and bronchoaveolar lavage fluids can also be used in certain patient conditions if the laboratory has validated specific specimen types.	
What are the requirements for testing?	Molecular testing must be performed in a Clinical Laboratory Improvement Amendments (CLIA) or CAP-accredited laboratory. There are several molecular tests that have received authorization for emergency use by the Food & Drug Administration (FDA). Most molecular tests authorized as Emergency Use Authorization (EUA) by the FDA are classified as moderate or high complexity. A few point-of-care tests have received FDA EUA authorization for use as a waived test. View a current list of tests with EUA authorization	Testing must be performed in a CLIA or CAP-accredited laboratory. The number of serology tests that have received FDA EUA authorization is increasing. Currently all the tests that are FDA EUA authorized are classified as moderate or high complexity.
Describe the test and what happens in the laboratory?	A molecular test (also called nucleic acid or RNA test) that uses the detection of nucleic acid, like RNA or DNA. Current authorized molecular tests are performed using polymerase chain reaction (PCR), which can amplify a small part of the virus RNA sequence billions-of-fold higher to allow detection with a fluorescence measuring instrument or other amplification methods such as isothermal amplification.	Blood samples are used to detect if a person has antibodies to SARS-CoV-2. The test detects antibodies, a blood protein produced in response to and counteracting a specific antigen like SARS-CoV-2.
What are the pros?	Very accurate. Test is highly sensitive, allowing for early detection days after infection. Looks for active infection.	More useful for determining if someone has had the infection or was exposed to the virus with or without symptoms.

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		The potential roles for COVID-19 serology tests include: • Identification of convalescent plasma donors; • Providing data on seroprevalence of SARS-CoV-2 infection; • Identification if an individual has been infected in the past; and • Verification of vaccine response once more is known about immunity Serology tests will detect a person who has been exposed to SARS-CoV-2 but can't determine if they had an active infection or was just exposed to the virus (asymptomatic). There is no data currently available that ensures that the presence of antibodies indicates immunity and, if so, for how long.
What are the cons?	Most molecular tests have a turn-around time of less than 24 hours but may take longer depending on where the testing is performed and the methodology. Molecular tests can provide a false-negative result if the viral load is too low for detection.	The antibody tests are an effort to detect whether a person had been infected with the virus, but results have been widely variable, and little is known about whether those who became ill will develop immunity and, if so, for how long. Depending on when the test is administered, a false-negative result could be reported if the test is obtained too early following infection. Laboratories should ask test manufacturers if they performed antibody specificity studies to assess for cross-reactivity to other viral antibodies, particularly antibodies to other coronaviruses which can cause a common cold. If these studies have

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		not been performed, there is a potential for false positive results. There is variability in available tests. Some test for Immunoglobulin M (IgM)*, some for Immunoglobulin G (IgG)** and some for total antibody. Some tests provide only a qualitative result while others provide titer information. **IgM: Found mainly in blood and lymph fluid, this is the first antibody the body makes when it fights a new infection.* *****IgG: Most common antibody. It's in blood and other body fluids and protects against bacterial and viral infections. IgG can take time to form after an infection or immunization.***
Why aren't more tests available?	The difficulties in increasing the number of tested by nucleic acid detection tests stem from many factors, including limited supplies of tests and reagents and limited supplies needed for testing (such as nasal swabs or RNA purification kits).	Serology testing is becoming more readily available. The number of FDA EUA authorized tests is increasing. Laboratories should refer to the FDA website for information on EUA authorized tests.
How is the FDA involved with testing?	Laboratories subject to US regulations may use the following types of tests as described in FDA's Policy for Diagnostic Tests for Coronavirus Disease-2019 during the Public Health Emergency: 1. Tests authorized through the FDA EUA process (that makes available diagnostic and therapeutic medical devices to diagnose and respond to public health emergencies).	There are several serology tests kits being marketed that have not been FDA EUA approved or sought EUA approval. The FDA recently updated its Policy for Diagnostic Tests for Coronavirus Disease-2019 during the Public Health Emergency to require commercial serology test manufacturers to apply for an EUA authorization from the FDA within a defined timeframe.

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	2. Tests developed by the laboratory with submission to the FDA for EUA 3. Test 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 authorization under the conditions defined in the Policy mentioned above. View a current list of tests with EUA authorization	View a current list of tests with EUA authorization
How is the Centers for Medicare and Medicaid Services (CMS) involved with testing?	CMS regulates all laboratory testing (except research) performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA). Laboratories must be accredited to perform testing and CMS oversees laboratory accreditation. The College of American Pathologists accredits laboratories having deemed status from CMS.	CMS regulates all laboratory testing (except research) performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA). Laboratories must be accredited to perform testing and CMS oversees laboratory accreditation. The College of American Pathologists accredits laboratories having deemed status from CMS.
What validation or verification is required for this testing?	Laboratories using an unmodified EUA test kit must verify the test method performance specifications (accuracy, precision, reportable range, and reference intervals), as applicable at their own laboratory prior to beginning patient testing. The laboratory may use information published in the manufacturer's package insert and other published literature for some aspects of the study (eg, interferences). For more specifics, the CAP offers detailed guidance.	Laboratories using an unmodified EUA test kit must verify the test method performance specifications (accuracy, precision, reportable range, and reference intervals), as applicable at their own laboratory prior to beginning patient testing. The laboratory may use information published in the manufacturer's package insert and other published literature for some aspects of the study (eg, interferences). For more specifics, the CAP offers detailed guidance.

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Additional commentary	Tests to detect SARS-CoV-2 antigen are beginning to come to market, but the clinical performance characteristics of these antigen tests have not been well studied, yet. Often, direct antigen assays have lower sensitivity than nucleic acid amplification tests.	It is important for clinical laboratories to understand and communicate to providers that COVID-19 serology tests are currently not recommended as an acute diagnostic and should not replace molecular tests on upper respiratory specimens for diagnosis. The timing and degree of immune response to COVID-19 is not yet fully understood, and serology tests will be negative prior to development of antibodies which can take several days after infection with the virus. Additionally, laboratories should ask test manufacturers if they performed antibody specificity studies to assess for cross-reactivity to other viral antibodies, particularly antibodies to other coronaviruses which can cause a common cold. If these studies have not been performed, there is a potential for false positive results. Ultimately, high specificity is a key component of any serologic test and rigorous clinical validation studies should be performed prior to use of these assays.

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