Testing for SARS-CoV-2 Infection

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<table>
<thead>
<tr>
<th>Summary of Testing for SARS-CoV-2 Infection</th>
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<td>The COVID-19 Treatment Guidelines Panel (the Panel) defers to the Centers for Disease Control and Prevention (CDC) for recommendations on diagnostic testing for SARS-CoV-2 infection. The Panel also defers to the CDC for recommendations on the use of testing for screening purposes, such as for screening among people who are asymptomatic but have had recent known or suspected exposure to SARS-CoV-2. Some key CDC recommendations include:</td>
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<td>• For diagnosing current SARS-CoV-2 infection, the CDC recommends using either a nucleic acid amplification test (NAAT) or an antigen test and using a specimen from the upper respiratory tract (e.g., nasal, nasopharyngeal).</td>
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<td>• There may be a window period of up to 5 days after exposure before viral antigens or nucleic acids can be detected.</td>
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<td>• NAATs are the most sensitive tests for detecting current SARS-CoV-2 infection. Because antigen tests are less sensitive than NAATs, the Food and Drug Administration recommends repeating antigen tests that produce negative results in certain circumstances, such as when clinical suspicion of COVID-19 is high in people who are symptomatic or when people who are asymptomatic have had known or suspected exposure to SARS-CoV-2.</td>
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<td>• Antibody tests should not be used to diagnose current SARS-CoV-2 infection.</td>
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<td>• Currently, antibody tests are not recommended for assessing SARS-CoV-2 immunity following COVID-19 vaccination or for assessing the need for vaccination in a person who is unvaccinated.</td>
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Diagnostic Testing for SARS-CoV-2 Infection

For diagnosing current SARS-CoV-2 infection, the Centers for Disease Control and Prevention (CDC) recommends using either a nucleic acid amplification test (NAAT) or an antigen test.\(^1\) Testing may also be used for screening and to determine the length of a patient’s isolation period.\(^2\) There may be a window period of up to 5 days after exposure before viral antigens or nucleic acids can be detected.

A number of diagnostic tests for SARS-CoV-2 infection (e.g., NAATs, antigen tests) have received Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs) for use in laboratories and points of care (e.g., physician offices, pharmacies, long-term care facilities, school clinics) and for self-administered testing.\(^3\) An influenza and SARS-CoV-2 multiplex NAAT that can simultaneously detect and differentiate between influenza A, influenza B, and SARS-CoV-2 also received an EUA from the FDA.\(^4\) The FDA also granted authorization to market the first over-the-counter, at-home, molecular NAAT (i.e., Cue COVID-19) and antigen test (i.e., Flowflex COVID-19) for use in people with symptomatic COVID-19.

For diagnosing current SARS-CoV-2 infection, the CDC recommends using a specimen from the upper respiratory tract (e.g., nasal, nasopharyngeal).\(^5\) Testing lower respiratory tract specimens is also an option in certain circumstances (e.g., in those receiving mechanical ventilation). For details about collecting and handling specimens for COVID-19 testing, please refer to the CDC’s recommendations.

Antigen Testing for SARS-CoV-2 Infection

Antigen-based diagnostic tests are widely used at home, at the point of care, and in the laboratory because of their low cost, rapid turnaround time, and availability. Antigen tests and laboratory-based NAATs have similar high specificity. False positive test results can occur with antigen tests, although they are unlikely when the tests are used correctly.\(^6\) The likelihood of a false positive antigen test result is higher when the expected probability of SARS-CoV-2 infection is low. Because antigen tests are less sensitive than NAATs, the FDA recommends repeating antigen tests that produce negative results in certain
circumstances, such as when clinical suspicion of COVID-19 is high in people who are symptomatic or when people who are asymptomatic have had known or suspected exposure to SARS-CoV-2.

**Nucleic Acid Amplification Testing for SARS-CoV-2 Infection**

NAATs, such as reverse transcription polymerase chain reaction–based diagnostic tests, which detect viral nucleic acids, are the most sensitive tests for detecting current SARS-CoV-2 infection.

Diagnostically, some NAATs may produce false negative results if a mutation occurs in the part of the virus’s genome that is assessed by that test. The FDA monitors the potential effects of SARS-CoV-2 genetic variations on NAAT results and issues updates when specific variations could affect the performance of NAATs that have received EUAs. A single negative test result does not exclude the possibility of SARS-CoV-2 infection in people who have a high likelihood of infection based on their exposure history or clinical presentation.

**Reinfection**

Reinfection has been reported in people after an initial diagnosis of SARS-CoV-2 infection. Because reinfection can be difficult to distinguish from persistent shedding (i.e., positive NAAT results persisting for weeks or months), the CDC recommends using an antigen test instead of a NAAT in patients who have symptoms compatible with SARS-CoV-2 infection who are within 90 days of recovering from a previous SARS-CoV-2 infection. Because intermittent detection of viral RNA can occur, a negative result on an initial NAAT followed by a positive result on a subsequent test does not necessarily mean a person has been reinfected. When the results for an initial and subsequent test are positive, comparative viral sequence data from both tests are needed to distinguish between the persistent presence of viral fragments and reinfection. In the absence of viral sequence data, the cycle threshold (Ct) value from a positive NAAT result may provide information about whether a newly detected infection is related to the persistence of viral fragments or to reinfection. The Ct value is the number of PCR cycles at which the nucleic acid target in the sample becomes detectable. In general, the Ct value is inversely related to the SARS-CoV-2 viral load. Because the clinical utility of Ct values is unclear, an expert should be consulted if these values are used to guide clinical decisions.

**Serologic or Antibody Testing for Diagnosis of SARS-CoV-2 Infection**

Unlike NAATs and antigen tests, which detect the presence of SARS-CoV-2, serologic or antibody tests can detect recent or prior SARS-CoV-2 infection or vaccination. The CDC recommends that antibody tests should not be used to diagnose current SARS-CoV-2 infection. It may take 21 days or longer after symptom onset for seroconversion to occur (i.e., the development of detectable immunoglobulin M or immunoglobulin G antibodies to SARS-CoV-2).

No serologic tests for SARS-CoV-2 have been approved by the FDA. Some, but not all, commercially available serologic tests for SARS-CoV-2 have received EUAs from the FDA. Several professional societies and federal agencies, including the Infectious Diseases Society of America, the CDC, and the FDA, provide guidance on the use of serologic testing for SARS-CoV-2.

**Serologic Testing and Immunity to SARS-CoV-2 Infection**

Currently, antibody tests are not recommended for assessing SARS-CoV-2 immunity following COVID-19 vaccination or for assessing the need for vaccination in a person who is unvaccinated.

The FDA has issued EUAs for more than 80 SARS-CoV-2 serologic tests since the beginning of the pandemic. However, these tests are not currently authorized for routine use in making individual medical decisions. SARS-CoV-2 serologic tests are authorized for detecting antibodies, but their
ability to predict protective immunity has not been validated. Most of these tests are not standardized. Furthermore, as SARS-CoV-2 is not a well-conserved virus, mutations in the receptor binding domain of the virus could lead to decreased binding affinity between antibodies and SARS-CoV-2–specific antigens.

If a serologic test is performed, the result should be interpreted with caution. First, it remains unclear how long SARS-CoV-2 antibodies persist following infection or vaccination. A negative serologic test result also does not preclude prior SARS-CoV-2 infection or vaccination against COVID-19. Second, some people who are infected with SARS-CoV-2 or who are vaccinated against COVID-19 (e.g., those who are immunocompromised) may not develop measurable levels of antibodies. It is presumed that those who do not have measurable antibodies after vaccination are at higher risk of SARS-CoV-2 infection than those who have measurable antibodies. Third, because nucleocapsid proteins are not a constituent of the vaccines that are currently approved by the FDA, available through EUAs, or in late-stage clinical trials, serologic tests that detect antibodies by recognizing nucleocapsid proteins should be used to distinguish between antibody responses to natural infection and vaccine-induced antibody responses to the SARS-CoV-2 spike protein antigen.

Assuming that the test is reliable, serologic tests that identify recent or prior SARS-CoV-2 infection may be used to determine who may be eligible to donate COVID-19 convalescent plasma and may aid in diagnosing multisystem inflammatory syndrome in children (MIS-C) and multisystem inflammatory syndrome in adults (MIS-A).

References


