Shasta County Health & Human Services Agency | Public Health Branch

Antigen (SARS-CoV-2) test overview and performance

June 9, 2021

Antigen tests are immunoassays that directly detect fragments of SARS-CoV-2 viral protein (antigen, as opposed to viral RNA detected by nucleic acid amplification tests [NAAT aka PCR tests]).Antigen tests are approved by the FDA for use on symptomatic individuals, and asymptomatic individuals either without or with known exposure.

The main advantages of antigen tests are fast turnaround time (approximately 15 minutes), simple to perform point-of-care use, identification of current viral infection, and lower cost. The current authorized antigen tests are not restricted to use on persons of a certain age.

The main drawbacks of antigen tests are lower sensitivity (more false negatives). The "gold standard" for clinical diagnostic detection of SARS-CoV-2 remains NAATs, such as RT-PCR. Thus, it may be necessary to confirm an antigen test result with a nucleic acid amplification test, especially if the result of the antigen test is inconsistent with the clinical context.

Positive results in symptomatic individuals are likely to reflect an active infection, but negative tests are presumptive negative and depending on level of clinical concern may need to be confirmed with a NAAT/PCR within 48 hours. A negative antigen test may not exclude infection and is of insufficient sensitivity to make decisions about isolation.

Positive results in asymptomatic individuals with or without known exposure to COVID-19 should be confirmed by NAAT/PCR and should quarantine while awaiting results of confirmatory testing.

In individuals with known exposure to COVID-19, a negative test indicates no current evidence of infection, but quarantine remains necessary in unvaccinated or symptomatic individuals until criteria are met for release from quarantine. Negative results in symptomatic individuals should be confirmed by NAAT/PCR.

Any NAAT confirmatory test of an antigen test result should be performed within 48 hours of the original antigen tests. Confirmatory tests performed more than 48 hours after the original antigen test should be considered a separate test. If an antigen test is used outside the recommended window from symptom onset or to test asymptomatic individuals, false positive results can occur. Depending on the level of tolerance for potential false positive results, confirmatory NAAT may be indicated.

The U.S. Food and Drug Administration (FDA) maintains a list of in vitro diagnostic tests for COVID-19 that are approved under an Emergency Use Authorization (EUA).

It is important to follow the manufacturer's instructions for accurate test results. Persons performing the point-of-care antigen test must be trained to perform the test following the manufacturer's Instructions for Use.

The clinical performance of antigen diagnostic test largely depends on circumstances in which they are used. Both antigen tests and NAATs perform best when the person is tested when viral load is generally highest.

Considerations for use of Molecular, Antigen, and Antibody Tests

	Molecular	Antigen	Antibody
Sample type	Usually nasopharyngeal (NP), oropharyngeal (OP), nasal mid-turbinate, or anterior nares swab. Other specimen types are possible such as saliva or wash	Usually NP or nasal swab	Blood-based test
What does it test	Amplifies specific fragment of viral RNA	Detects fragments of viral proteins	Measures antibody response to viral protein target
When to test	Most likely to be positive 1-2 days before symptom onset and in early days of symptomatic infection	5-7 days after symptom onset, depending on type of test being used	Take at least 7-14 days after symptom onset to develop antibodies, and varies depending on antibody class being measured
How well does it work	Sensitivity varies depending on sampling technique and specimen type, but highly specific	Very specific for the virus, but not as sensitive as PCR	Both sensitivity and specificity are highly variable depending on type of test; not a diagnostic tool
When to use	Anyone who does or does not have COVID-19 symptoms to help identify those who might be infectious	Anyone who does or does not have COVID-19 symptoms to help identify those who might be infectious, confirmatory testing might be advised	Surveillance of a population—assessing how many people in the population have been infected with COVID-19
Who can collect the specimen*	Trained healthcare personnel* or supervised self-collection	Trained healthcare personnel* or supervised self-collection	Trained healthcare personnel*
How long does it take to get results	1-7+ days	15 minutes or less	10 minutes to 3+ days
How results are used	Helps identify people with current infection and recommend isolation to prevent the spread of illness	Helps identify people with current infection and recommend isolation to prevent the spread of illness	Helps to determine prevalence of past infection

*Trained healthcare personnel

- Physicians
- Physician assistants
- Registered nurses
- Licensed vocational nurses
- Psychiatric technicians
- EMTs & Paramedics
- Respiratory care practitioners
- Medical assistants (front of nose only)
- Phlebotomists (antibody only)

References and more information: CDC; CDPH; FDA

Regulatory Requirements

Sites that perform Point of Care (POC) antigen tests are required to have a Clinical Laboratory Improvement Amendments (CLIA) Certificate. There are four different types of CLIA certificates, any one of which is appropriate for POC testing. See this Centers for Medicare & Medicaid Services (CMS) document that describes the different types of CLIA certificates. A CLIA Certificate of Waiver is appropriate for POC testing and can be obtained as follows:

1. Complete an application (Form CMS-116), available on the CMS CLIA website or from the California Department of Public Health (CDPH).
2. Send the completed application to CDPH.
3. Pay the CLIA Certificate of Waiver fee, following instructions provided by CDPH.

Further information on obtaining a CLIA Certificate of Waiver may be found here. POC testing may be performed after the testing site has received a CLIA certificate number. The testing site must keep its certificate information current. CDPH should be notified of any changes in ownership, name, address, or director within 30 days.

Reporting of antigen test results

- Any facility approved to test for SARS-CoV-2 must report all positive and non-positive (negative, indeterminate, and specimen unsatisfactory) test results from nucleic acid amplification tests (e.g., PCR) and antibody/serology tests for SARS-CoV-2 through the CalREDIE Electronic Laboratory Reporting system (ELR) or the Manual Laboratory Reporting Module within eight hours from the time the laboratory notifies the health care provider or other person authorized to receive the report. Laboratories must report data on patients' race and ethnicity for all COVID-19 test results.
- Laboratories conducting SARS-CoV-2 antigen testing that are not reporting antigen test results through the CalREDIE Electronic Laboratory Reporting system (ELR) must report aggregate test results for non-positive (negative, indeterminate, specimen unsatisfactory) daily via the Daily Antigen Survey. Information on the survey is available here: How to Complete the Daily Antigen Survey (ca.gov) (PDF). If not reporting positive tests via ELR, laboratories must notify SCPH via fax at 530-225-5074.

Evaluating the Results of Antigen Testing for SARS-COV-2

Evaluating the results of an antigen test for SARS-CoV-2 should take into account the performance characteristics (e.g., sensitivity, specificity) and the instructions for use of the FDA-authorized assay, the prevalence of SARS-CoV-2 infection in that particular community (positivity rate over the previous 7–10 days or the rate of cases in the community), and the clinical and epidemiological context of the person who has been tested.

It may be appropriate to confirm antigen test results with another test. CDC recommends following its antigen testing algorithm (Figure 1 below to determine when confirmatory testing is recommended).

The evaluation of an antigen test result should consider whether, and if so the length of time, the patient has experienced symptoms. Generally, clinicians can rely upon a positive antigen test result for a symptomatic patient because the specificity of current FDA-authorized antigen tests is high.

The sensitivity of current FDA-authorized antigen tests varies, and thus negative diagnostic testing results should be handled differently depending on the test, its stated performance characteristics, and intended application (e.g., clinical diagnosis, screening). In most cases, the manufacturers' instructions for use of

antigen tests indicate that negative test results should be considered “presumptive,” meaning that they are preliminary results. See FDA’s In Vitro Diagnostics EUAs.

It may be appropriate to confirm antigen test results with another test. CDC recommends following its antigen testing algorithm (Figure 1 below to determine when confirmatory testing is recommended). For more information regarding how to evaluate Results of Antigen Testing for SARS-COV-2 see more at the CDC’s website.

Resources

Food and Drug Administration. Performance characteristics of EUA-approved assays have been published in the "Instructions for Use" links on the FDA website.

Ramdas K, Darzi A, Jain S. 'Test, re-test, re-test': using inaccurate tests to greatly increase the accuracy of COVID-19 testing. Nat Med. 2020;26(6):810-811. doi:10.1038/s41591-020-0891-7

California Department of Public Health Guidance on the Use of Antigen Tests for Diagnosis of Acute COVID-19. https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/COVID-19/CDPH-Guidance-on-the-Use-of-Antigen-Tests-for-Diagnosis-of-Acute-COVID-19.aspx#

Considerations for Implementation of SARS-CoV-2 Rapid Antigen Testing. Association of Public Health Laboratories. https://www.aphl.org/programs/preparedness/Crisis-Management/Documents/APHL-SARSCov2-Antigen-Testing-Considerations.pdf

Considerations for Interpreting Antigen Test Results in Nursing Homes. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/downloads/hcp/nursing-home-testing-algorithm-508.pdf

Considerations for Use of SARS-CoV-2 Antigen Testing in Nursing Homes. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/nursing-homes-antigen-testing.html

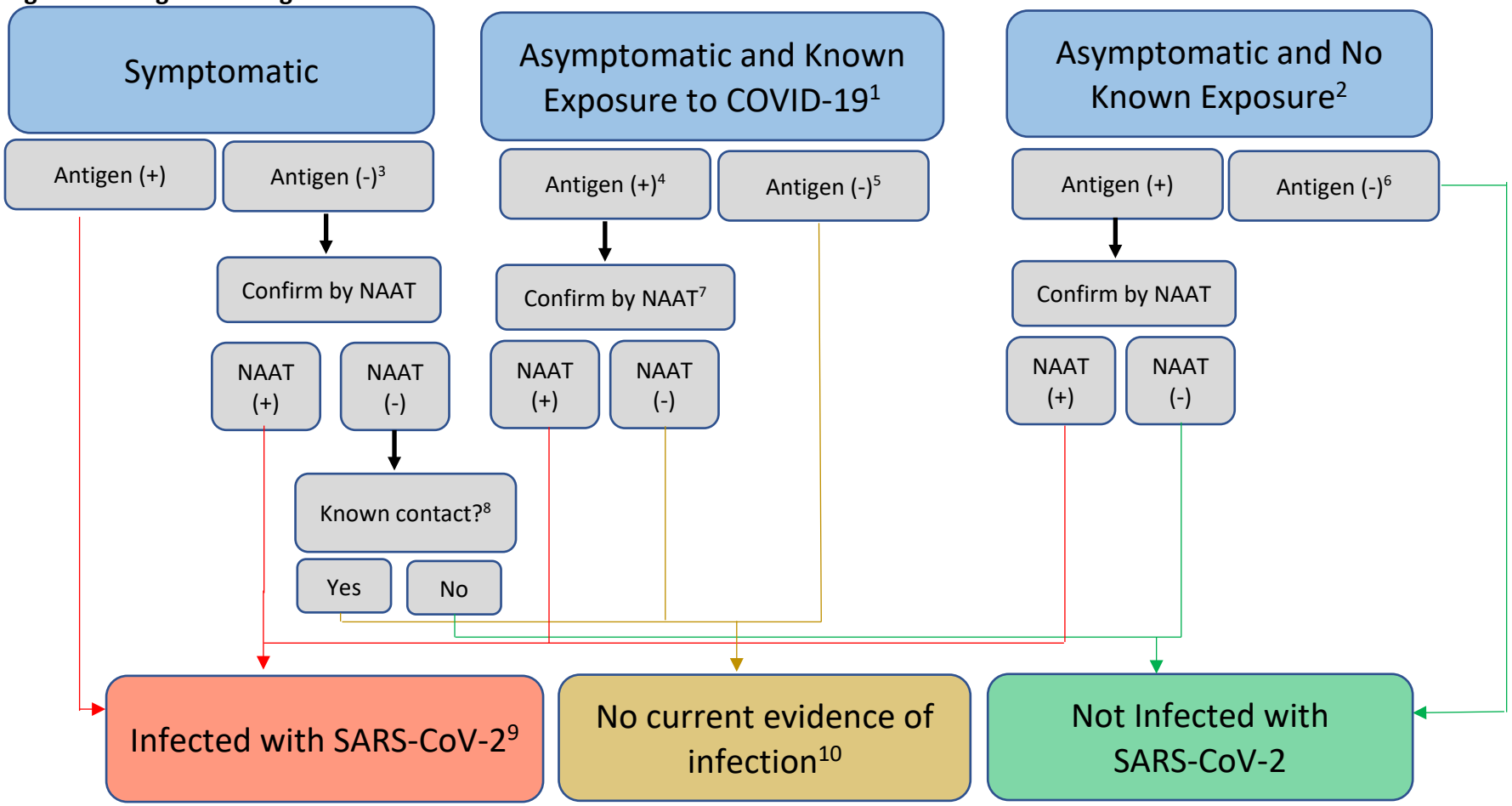
Interim Guidance for Rapid Antigen Testing for SARS-CoV-2. Centers for Disease Control. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html

Guidance for SARS-CoV-2 Point-of-Care Testing. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/lab/point-of-care-testing.html

Interim Considerations for Testing for K-12 School Administrators and Public Health Officials. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/k-12-testing.html

Interim Guidance on Unsheltered Homelessness and Coronavirus Disease 2019 for Homeless Service Providers and Local Officials. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/community/homeless-shelters/unsheltered-homelessness.html

Figure 1. Antigen Test Algorithm



[1] Single, multiple, or continuous known exposure to a person with COVID-19 within the last 14 days; perform NAAT first if short turnaround time is available, if person cannot be effectively and safely quarantined, or if there are barriers to possible confirmatory testing.

[2] No known exposure to a person with COVID-19 within the last 14 days.

[3] If a symptomatic person has a low likelihood of SARS-CoV-2 infection, clinical discretion should determine if this negative antigen test result requires confirmatory testing. [4] In instances of higher pretest probability, such as high incidence of incidence of infection in the community, clinical discretion should determine if this positive antigen result requires confirmation.

[5] In certain settings, serial antigen testing could be considered for those with a negative antigen test result; serial testing may not require confirmation of negative results. The role of a negative antigen test result in ending quarantine depends upon when it is performed in the quarantine period. See CDC's Options to Reduce Quarantine for guidance on use of antigen testing for this purpose and when a negative antigen test result indicates not infected with SARS-CoV-2.

[6] If prevalence of infection is not low in the community, clinical discretion should consider whether this negative antigen result requires confirmation.

[7] Nucleic acid amplification test; confirm within 48 hours using a NAAT, such as RT-PCR, that has been evaluated against FDA's reference panel for analytical sensitivity.

[8] Known exposure to a person with COVID-19 within the last 14 days; if unsure, clinical discretion should determine whether isolation is necessary.

[9] Isolation is necessary. See CDC's guidance for Isolation.

[10] Quarantine is necessary. See CDC's guidance for Quarantine; clinical discretion should determine if and when additional testing is necessary. Fully Vaccinated* can refrain from quarantine and testing following a known exposure if asymptomatic.

*Fully vaccinated for COVID-19 ≥2 weeks after they have received the second dose in a 2-dose series (Pfizer-BioNTech or Moderna), or ≥2 weeks after they have received a single-dose vaccine (Johnson and Johnson (J&J)/Janssen