Potential for False Positive Results with Antigen Tests for Rapid Detection of SARS-CoV-2 - Letter to Clinical Laboratory Staff and Health Care Providers

The U.S. Food and Drug Administration (FDA) is alerting clinical laboratory staff and health care providers that false positive results can occur with antigen tests, including when users do not follow the instructions for use of antigen tests for the rapid detection of SARS-CoV-2. Generally, antigen tests are indicated for the qualitative detection of SARS-CoV-2 antigens in authorized specimen types collected from individuals who are suspected of COVID-19 by their healthcare provider within a certain number of days of symptom onset. The FDA is aware of reports of false positive results associated with antigen tests used in nursing homes and other settings and continues to monitor and evaluate these reports and other available information about device safety and performance.

The FDA reminds clinical laboratory staff and health care providers about the risk of false positive results with all laboratory tests. Laboratories should expect some false positive results to occur even when very accurate tests are used for screening large populations with a low prevalence of infection. Health care providers and clinical laboratory staff can help ensure accurate reporting of test results by following the authorized instructions for use of a test and key steps in the testing process as recommended by the Centers for Disease Control and Prevention (CDC), including routine follow-up testing (reflex testing) with a molecular assay when appropriate, and by considering the expected occurrence of false positive results when interpreting test results in their patient populations.

Recommendations

The FDA recommends clinical laboratory staff and health care providers who use antigen tests for the rapid detection of SARS-CoV-2:

- Be aware that the Conditions of Authorization in the antigen Emergency Use Authorizations specify that authorized laboratories are to follow the manufacturer's instructions for use, typically found in the package insert, when performing the test and reading test results. If you no longer have the package insert for the test you are using, you can contact the manufacturer. The authorized instructions for use for each test can also be found on the FDA's COVID-19 IVD EUA webpage (/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas).
    - For example, the package insert for tests include instructions for handling of the test cartridge/card, such as ensuring it is not stored open prior to use. If the test

components are not stored properly, this can affect the performance of the test.

- The package insert for tests also includes instructions about reading the test results, including the appropriate time to read the results. **Reading the test *before or after* the specified time could result in false positive or false negative results.**

- Be aware that processing multiple specimens in batch mode may make it more challenging to ensure the correct incubation time for each specimen. Refer to the package insert and ensure proper timing for each specimen when processing the specimen in the test device and reading the results.
- Be careful to minimize the risks of cross-contamination when testing patient specimens, which can cause false positive results. Insufficient cleaning of the workspace, insufficient disinfection of the instrument, or inappropriate use of protective equipment (for example, failing to change gloves between patients) can increase the risk of cross-contamination between specimens with subsequent false positive results. Consider the CDC guidance (https://www.cdc.gov/coronavirus/2019-ncov/lab/point-of-care-testing.html) for changing gloves and cleaning work area between specimen handling and processing.
- Consider the CDC's recommendations (https://www.cdc.gov/coronavirus/2019-ncov/hcp/nursing-homes-antigen-testing.html) when using antigen testing in nursing homes and other settings. For positive results, especially in low incidence counties, consider performing confirmatory RT-PCR test within 48 hours.
- Remember that positive predictive value (PPV) varies with disease prevalence when interpreting results from diagnostic tests. PPV is the percent of positive test results that are true positives. As disease prevalence decreases, the percent of test results that are false positives increase.
    - For example, a test with 98% specificity would have a PPV of just over 80% in a population with 10% prevalence, meaning 20 out of 100 positive results would be false positives.
    - The same test would only have a PPV of approximately 30% in a population with 1% prevalence, meaning 70 out of 100 positive results would be false positives. This means that, in a population with 1% prevalence, only 30% of individuals with positive test results actually have the disease.
    - At 0.1% prevalence, the PPV would only be 4%, meaning that 96 out of 100 positive results would be false positives.
    - Health care providers should take the local prevalence into consideration when interpreting diagnostic test results.
- Consider positive results in combination with clinical observations, patient history, and epidemiological information.

- Be aware that the Conditions of Authorization in the antigen EUAs specify that Authorized Laboratories are to collect information on the performance of antigen tests and report any suspected occurrence of false positive or false negative results and significant deviations from the established performance characteristics of which they become aware to both the FDA and the test manufacturer.

Background

The FDA issued the first Emergency Use Authorization (EUA) for a COVID-19 antigen test in May 2020. These diagnostic tests quickly detect fragments of proteins found on or within the virus by testing samples collected from the nasal cavity using swabs. A list of the FDA-authorized antigen tests are available on the FDA's In Vitro Diagnostics EUA page (https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#individual-antigen).

Antigen tests are an important tool in the overall response against COVID-19 and benefit public health. One of the main advantages of an antigen test is the speed of the test, which can provide results in minutes. The availability of these types of tests may provide the ability to test millions of Americans rapidly.

In general, antigen tests are not as sensitive as molecular tests. Due to the potential for decreased sensitivity compared to molecular assays, negative results from an antigen test may need to be confirmed with a molecular test prior to making treatment decisions. Negative results from an antigen test should be considered in the context of clinical observations, patient history and epidemiological information.

Like molecular tests, antigen tests are typically highly specific for the SARS-CoV-2 virus. However, all diagnostic tests may be subject to false positive results, especially in low prevalence settings. Health care providers should always carefully consider diagnostic test results in the context of all available clinical, diagnostic and epidemiological information. Test interference from patient-specific factors, such as the presence of human antibodies (for example, Rheumatoid Factor, or other non-specific antibodies) or highly viscous specimens could also lead to false positive results.

FDA Actions

The FDA continues to work with other agencies, such as the Centers for Disease Control and Prevention (CDC) and the Centers for Medicare and Medicaid Services (CMS) to safeguard COVID test use in nursing homes and other settings.

The FDA is also working with test manufacturers to ensure that their instructions for use are as clear as possible to minimize the occurrence of false results.

The FDA will continue to keep clinical laboratory staff, health care providers, manufacturers, and the public informed of new or additional information.

Additional Resources

- CDC's Considerations for Use of SARS-CoV-2 Antigen Testing in Nursing Homes (https://www.cdc.gov/coronavirus/2019-ncov/hcp/nursing-homes-antigen-testing.html)
- FAQs on Testing for SARS-CoV-2 (/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2)
- In Vitro Diagnostics EUAs (/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas)

Reporting Problems to the FDA

The FDA encourages stakeholders to report any adverse events or suspected adverse events experienced with antigen tests for rapid detection of SARS-CoV-2.

- Voluntary reports can be submitted through MedWatch, the FDA Safety Information and Adverse Event Reporting program (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda).
- Generally, as specified in a test's EUA, device manufacturers must comply with applicable Medical Device Reporting (MDR) regulations (/medical-devices/postmarket-requirements-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities).
- Health care personnel and clinical laboratory staff employed by facilities that are performing COVID-19 testing should follow the reporting requirements for authorized laboratories as specified in the test's EUA.

Prompt reporting of adverse events can help the FDA identify and better understand the risks associated with medical devices.

Contact Information

If you have questions about this letter, contact COVID19DX@fda.hhs.gov (mailto:COVID19DX@fda.hhs.gov).