



Serological Testing for SARS-CoV-2 Antibodies

Overview

As COVID-19 continues to spread amongst the U.S. population, a number of new tests aimed at identifying those with prior exposure to COVID-19 are rapidly coming to market. These tests—serology tests—test for the presence of antibodies to the SARS-CoV-2 virus. Antibodies can be found in the blood of those who are tested after infection and typically show that a recovered individual has developed an immune response to the virus. These tests may play an important role in determining the overall prevalence of COVID-19 in the US population, and may also be important in determining the prevalence of asymptomatic infections. While these tests will undoubtedly play an important role in population-level studies going forward, they are not without limitation. The AMA cautions physicians and the general public about use of these tests to determine individual immunity and warns that public health decisions, such as discontinuation of physical distancing, should not be made on the basis of results.

Regulation

Laboratory tests, such as serological tests for SARS-Cov-2 antibodies, are regulated by the U.S. Food and Drug Administration (FDA) and also by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). FDA currently requires all commercially marketed serological tests to apply for and receive an Emergency Use Authorization (EUA) to market these tests to the public. FDA has also provided recommended performance standards that these tests should meet. However, FDA does not automatically independently verify performance of each of these tests and primarily relies on submitting manufacturers to self-validate their offerings. For tests that are not commercially marketed, such as laboratory developed tests (LDTs), FDA authorization is not required. However, these tests must be performed in a laboratory certified to perform high-complexity testing under CLIA. As of May 5, approximately 12 commercial serological tests have been granted EUAs, while over 120 tests are currently on the market.

Recently, concern has been growing over both test performance and fraudulent labeling of a number of currently marketed tests. While many tests with FDA authorization are relatively high-performing, a number of tests currently on the market are not. Tests showing lower performance will, unfortunately, return a significantly higher number of false results in our current state of low disease prevalence. This is particularly concerning when discussing false positive results, as they may lead individuals to think they are immune from COVID-19 when they are not. Further, FDA has taken action against a number of tests falsely labeled as FDA authorized when they have not been granted EUA status.

Limitations

Physicians and the general public need to be aware that serology tests have several inherent limitations that make correct interpretation of the results critical. Serological tests for SARS-CoV-2 antibodies present even greater challenges, as much is still unknown about immune status for the novel virus. Some limitations to be aware of include:

- **False Positive Results:** Serological testing for disease with a low prevalence in the population presents inherent challenges with interpretation of positive results. Even high performing tests (e.g. high sensitivity and specificity) will return false positive results when disease prevalence is low, as is currently the case with COVID-19. Take, for example, a community of 100 individuals

with a disease prevalence of 5 percent. If a serological test with a specificity of 95% was used in this population, it would be expected to return 5% false positives, so 5 out of the population of 100. Five true positives would also be expected, as the disease prevalence is 5 percent. Overall, this test would return 10 positive results, however, only 50% of the results would be accurate, showing the inherent limitation of these types of tests in low disease prevalence states. Once disease prevalence is higher, the concern about false positives becomes somewhat mitigated, however, this is not the current reality with COVID-19.

- **Cross-Reactivity:** While this may not be true of all serology tests for SARS-CoV-2, cross-reactivity has been a noted concern among some offered tests. Cross-reactivity occurs when a test for antibodies for SARS-CoV-2 identifies not only antibodies for this virus, but also for other coronaviruses, such as those causing the common cold. For tests where cross-reactivity is possible, antibodies for other coronaviruses may result in a positive test result for SARS-CoV-2 even when the patient in question was not infected.
- **Immune Status:** Given that SARS-CoV-2 is a novel virus, there is much we do not know about what, if any, immunity it may confer to those exposed and recovered from infection. According to the WHO, there is no currently available evidence showing immunity to COVID-19 after infection. While individuals typically develop some type of immune response after exposure to most viruses, it is not yet clear when an immune response develops after COVID-19 infection, how strong this immune response may be, and how long the immune response may last.

Recommendations

Physicians and the general public need to be well-versed in the limitations of serology tests in the current environment and have a strong understanding of both the tests and the potential results. This is particularly true for those caring for marginalized and minoritized patient-communities that are disproportionately impacted by COVID-19, or where access to testing services may be limited, or where housing or employment status of patients may make it difficult for them to adhere to physical distancing and other COVID-19 guidance precautions. The AMA has developed the following recommendations for consideration and use of the tests to help guide physicians and individuals considering using them:

- Use of serology tests should currently be limited to population-level seroprevalance study, evaluation of recovered individuals for convalescent plasma donations, and in other situations where they are used as part of a well-defined testing plan and in concert with other clinical information by physicians well-versed in interpretation of serology test results.
- Serology tests should not be offered to individuals as a method of determining immune status. Individuals receiving positive test results may falsely assume it is safe to discontinue physical distancing. The AMA recommends all Americans continue to abide by physical distancing recommendations and shelter in place requirements for so long as necessary to reduce the threat of COVID-19. Serology tests should not currently be used as the basis for any “immunity certificates,” to inform decisions to return to work, or to otherwise inform physical distancing decisions. Doing so may put individuals, their household, and their community at risk.
- Serology tests should not be used as the sole basis of diagnosis of COVID-19 infection.
- Physicians should pay close attention to the regulatory status of any test offered. FDA maintains a listing of all serological tests authorized for use for COVID-19 at <https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd>. Physicians should be aware of the performance characteristics of any test used and how those align with the FDA recommended performance standards. Physicians should note that there has been reported fraudulent marketing of some tests and should verify the regulatory status of these claims before incorporating them in to practice.

- Messaging on serological testing to medically underserved communities should explicitly take into consideration cultural and social features which may bear on their ability to make long-term choices on physical distancing and other COVID-19 precautions.

Resources:

FDA Policy on Serological Testing for COVID-19 (May 2020): <https://www.fda.gov/news-events/fda-voices/insight-fdas-revised-policy-antibody-tests-prioritizing-access-and-accuracy>

CDC on Serology Testing for COVID-19: <https://www.cdc.gov/coronavirus/2019-ncov/lab/serology-testing.html>

WHO on Immunity Passports: <https://www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19>