

April 28, 2020

Louisiana Health Alert: Considerations for use of serology testing for COVID-19

Given widespread demand for serology testing of COVID-19, and the lack of data on basic test features, the Louisiana Department of Health is issuing the following considerations for providers. These are directly quoted from guidance released by the Infectious Disease Society of America (IDSA).

BACKGROUND ON ANTIBODY TESTING FOR SARS-CoV-2 INFECTION

- The antibody response in infected patients remains largely unknown, and the clinical values of antibody testing have not been fully demonstrated. Seroprevalence data will be important in understanding the scale of the pandemic and future vaccine utility.
- Potential utility of serology in SARS-CoV-2:
 - Detection of PCR-negative cases, especially for patients who present late with a very low viral load below the detection limit of RT-PCR assays, or when lower respiratory tract sampling is not possible;
 - Identification of convalescent plasma donors;
 - Epidemiologic studies of disease prevalence in the community;
 - Verification of vaccine response once antibody correlate(s) of protection identified.
- Potential drawbacks if serological assays are not well-validated:
 - False negative risks if performed early in disease course, especially in mild disease;
 - False positive risks, particularly with tests for Immunoglobulin M (IgM) and potential cross-reactivity with common cold coronaviruses (e.g. HKU1, NL63, OC43, 229E).

TEST QUALITY & INTERPRETATION

- There are a multitude of different antibody tests for COVID-19 with variable performance. Tests vary in the viral antigen(s) they target, e.g., nucleoprotein (N protein) or spike protein (S protein). It is not yet clear which antibody responses, if any, are protective or sustained.
- A "positive" test is exceptionally difficult to interpret because the performance of these tests is not well known. For some assays both sensitivity and specificity may be poor, or at the very least undefined.
- Clinical laboratories will need to perform validation studies of commercial reagents.
- **Some FDA-authorized COVID-19 antibody tests are estimated to have 96-98% specificity, which would mean that a positive test result is more likely a false-positive result than a true positive result if the [prevalence](#) or pretest probability is 5% or less.**

ADDITIONAL CONSIDERATIONS

- No universal standard for reporting is available and test detection limits are variable. Some assays provide semi-quantitative results and others are designed to be qualitative (i.e. antibody detected or not).
- Combination IgG/IgM tests can provide unclear value given the potential for cross-reactivity with other coronavirus antibodies and the often-poor specificity of IgM.
- Currently available commercial assays do not have titers, and without this information it is unclear how to identify "qualified" individuals for plasma donation.

- Nucleic acid amplification tests (NAATs) perform differently than antibody testing, and this has implications for interpretation. The NAATs that were developed for SARS-CoV-2 are very specific. In patients with signs and symptoms of infection, a positive NAAT result has a very high positive predictive value (PPV) for true infection. Conversely, both the negative and PPV of antibody testing are likely to be lower, given the low prevalence of prior exposure to SARS CoV-2 in the U.S. population and imperfect sensitivity and specificity of the test.
- As a result, antibody tests will be most useful as surveillance tools to estimate (with surrounding confidence intervals) relative proportions of different populations that have been exposed to SARS CoV-2. They will have less utility as diagnostic tools for individual patient assessment.

Additionally, it is important to recognize the difference between an Emergency Use Authorization (EUA) and full marketing authorization from the FDA. Most of these tests approved under EUAs have not undergone the same rigorous review as if they had received full approval.

More information on approved serology tests has been compiled here:

<https://www.centerforhealthsecurity.org/resources/COVID-19/serology/Serology-based-tests-for-COVID-19.html>

The primary document from IDSA referenced above is available here: <https://www.idsociety.org/news--publications-new/articles/2020/emphasizing-need-for-more-information-idsa-releases-antibody-testing-primer2/>