5-27-2020

Current Status of Serologic Testing for Covid-19

George Washington University

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Date: May 27, 2020

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Summary: The GW COVID-19 Intelligence Unit was asked to summarize the current state of serologic testing for antibodies against SARS-CoV-2. The resulting summary reflects up-to-date resources, including primary papers, expert opinion, and the recently released *IDSA Guidelines on the Diagnosis of COVID-19* as well as *CDC Interim Guidelines for COVID-19 Antibody Testing.* As the current evidence base to inform the use of serologic testing is limited, expert consensus is that it is therefore premature to apply these tests broadly for decisions in clinical management, health resource utilization, or public policy.

Key points:

- **Serologic tests** detect the presence of antibodies generated by the body's adaptive immune response to the virus. This response and its detection may vary by:
    - Patient factors including age group, medical condition, medications, and others.
    - Viral antigens presented for immune recognition – spike and nucleocapsid proteins.
    - Method of detection – including point-of-care / rapid diagnostic tests (lateral flow assays) and laboratory tests (ELISA, neutralization, or chemiluminescent assays). These vary by complexity, turn-around time, throughput, and result reproducibility.
    - Timing of testing relative to exposure (see **Figure** at the end of document). Antibody response may be absent in early infection.
- **Type of antibodies:**
    - IgM – produced earlier in acute infection, found on B lymphocytes and in blood.
    - IgG – most abundant antibody, produced 2-3 weeks into infection; is key to neutralizing the pathogen and establishing long-lasting immunity.
    - IgA – primarily responsible for protecting mucosal surfaces.
- **Cross-reactivity** to common coronaviruses is of concern for all serologic tests.
- It is unknown to what degree **protective immunity** against future infection is conferred by the presence of IgG. Antibodies against other coronaviruses (including SARS and MERS) can persist for over a year after exposure but reinfections are observed with common coronaviruses. It is unknown if this is due to waning immunity or to viral genetic variation.
- In contrast to the RT-PCR tests, there is **no single "gold standard"** for antibodies to SARS-CoV-2, but numerous tests have been granted EUA status by the FDA.

    - The Johns Hopkins Center for Health Security keeps an up-to-date list of these.
    - Some assays report very high (99-100%) sensitivity and specificity, however criticisms of these have included lack of outside scrutiny and commercial COI.
    - Others report likely more realistic sensitivity and specificity (70%-96%).
    - Validation studies for these typically involve a small pre-selected patient sample.
    - Agreement between the tests can range widely (76-95% in study by UCSF and MGH).
- The **real-world clinical performance** (positive and negative predictive values) of these tests are dependent both on the sensitivity and specificity, and disease prevalence in a given population. **In a low-prevalence population, the risk of false-positive serologic tests is higher, even with excellent test specificity.** Some reported seroprevalence studies:
    - Boise, ID, April 2020: 1.8%
    - LA County, CA, April 2020: 4.65% (CI: 2.52%-7.07%)
    - New York, April 2020: 13.9% statewide and 21.2% in NYC (but with selection bias)
- The FDA initially allowed pre-review marketing of serologic tests for COVID-19 without EUA process, but changed the policy in late April to require review under a simplified process.

Summary of current recommendations:

- **Serologic tests may be used for:**
    - Epidemiologic studies
    - Identifying potential convalescent plasma donors
    - Evaluating the immune response to candidate vaccines
- **Serology testing should NOT be used for:**
    - Diagnosing acute or recent clinical cases of COVID-19
    - Attempting to determine if a patient has developed protective immunity.
    - Guiding personal PPE use, employment decisions, or adherence to social distancing

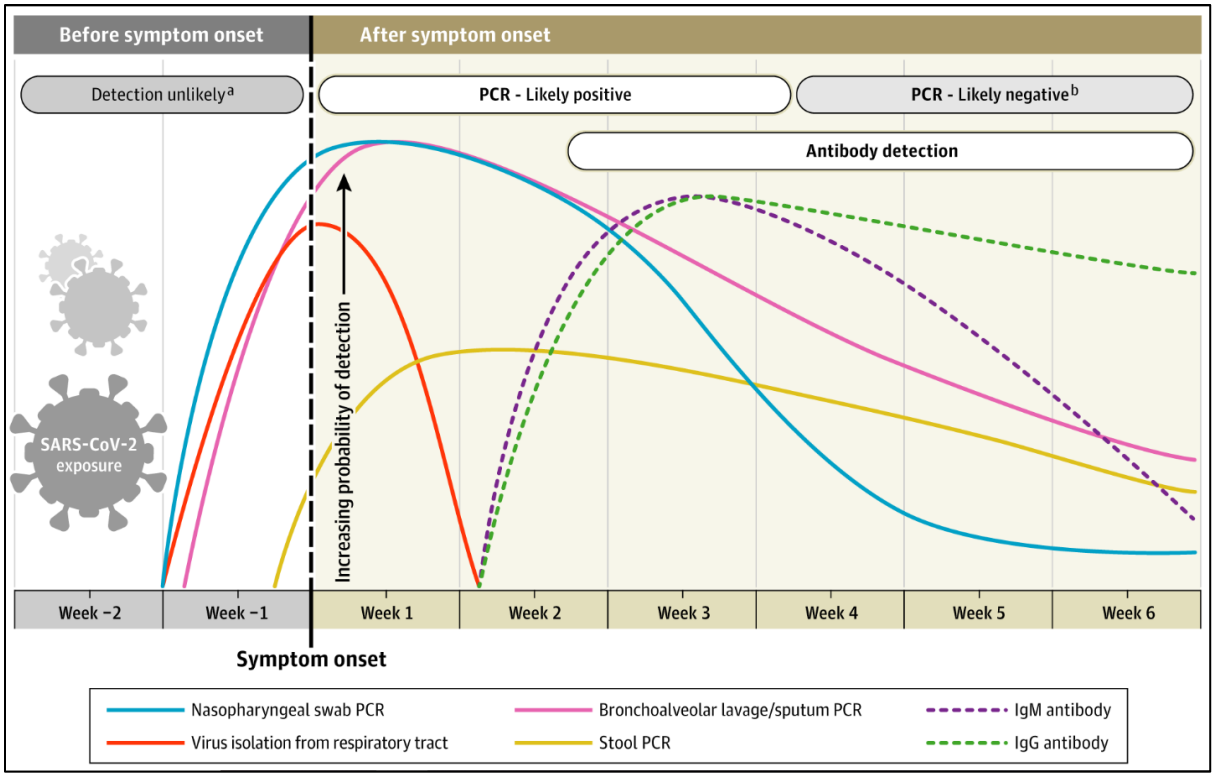

Figure (Source: Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. *JAMA*. 2020.)

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