Policy Number	**MED207.162**
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SARS-CoV-2 (COVID-19) Antibody Testing

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Antibody testing for the SARS-CoV-2 (COVID-19) virus **is considered experimental, investigational, and/or unproven** for all indications.

NOTE: Antibody testing for the SARS-CoV-2 (COVID-19) virus provided under an Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) during a public health emergency is **NOT** addressed by this policy.

Policy Guidelines

None.

Description

Human Coronavirus Types

Coronaviruses are named for the crown-like spikes on their surface. Human coronaviruses were first identified in the mid-1960s; and there are four main sub-groupings of coronaviruses – alpha, beta, gamma, and delta. There are seven coronaviruses that can infect humans:

1. 229E (alpha coronavirus);
2. NL63 (alpha coronavirus);
3. OC43 (beta coronavirus);
4. HKU1 (beta coronavirus);
5. MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS);
6. SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS); and
7. SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19).

According to the Centers for Disease Control and Prevention (CDC), people around the world are commonly infected with human coronaviruses 229E, NL63, OC43, and HKU1. Sometimes coronaviruses that infect animals can evolve and make people sick and become a new human coronavirus. Three recent examples of this are 2019-nCoV (also known as SARV-CoV-2 or COVID-19), SARS-CoV, and MERS-CoV. (1)

<u>SARs-CoV-2 Novel Coronavirus (COVID-19)</u>

The SARS-CoV-2 coronavirus, or COVID-19, first appeared in Wuhan, China, in December 2019. It quickly spread throughout the world, causing a world-wide pandemic. A novel coronavirus is a new coronavirus that has not been previously identified. The World Health Organization (WHO) announced the official name for the disease causing the 2019 novel coronavirus outbreak. The new name of this disease is coronavirus disease 2019, abbreviated as COVID-19. In COVID-19, 'CO' stands for 'corona,' 'VI' for 'virus,' and 'D' for disease. (2) Formerly, this disease was referred to as "2019 novel coronavirus" or "2019-nCoV". (3)

Variants

Like other viruses, SARS-CoV-2 has evolved over time. Most mutations in the SARS-CoV-2 genome have no impact on viral function although certain variants have received attention because of their rapid emergence within populations and evidence for transmission or clinical implications. Certain variants have evidence of an increase in transmissibility, greater risk of severe disease, a significant reduction in neutralization by antibodies generated during prior infection or vaccination, or reduced effectiveness of treatments or vaccines. Since 2022, Omicron (B.1.1.529) variants within evolving sub lineages have been the predominant circulating variants globally. Prior variants that are no longer circulating include the Alpha (B.1.1.7 lineage), Beta (B.1.351 lineage), Gamma (P.1 lineage), and Delta (B.1.617.2 lineage) variants. In the United States, circulating variants are monitored by the Center for Disease Control and prevention which can be viewed on the CDC website <https://covid.cdc.gov>. (3)

Symptoms

The virus causing COVID-19 is thought to spread primarily from person to person, mainly through respiratory droplets produced when an infected person talks, coughs, or sneezes. Those droplets can land in the mouths or noses of nearby people or possibly be inhaled into the

lungs. Another route of infection may also be by direct contact with a contaminated surface followed by touching the eyes, nose, or mouth although this is thought to not be the primary route of exposure. A wide range of symptoms have been reported, including but not limited to fever, cough, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, shortness of breath or difficulty breathing. (2, 3) Symptoms may appear 2 to 14 days after exposure to the virus. (1)

Long COVID

Some Individuals who have been infected with the virus that causes COVID-19 can experience long-term effects from their infection, known as Long COVID or Post-COVID conditions (PCC). Long COVID is broadly defined by the CDC and the Department of Health and Human Services as signs, symptoms, and conditions that continue or develop after acute COVID-19 infection. Long COVID can include a wide range of ongoing health problems; these conditions can last weeks, months, or years. Long COVID occurs more often in people who had severe COVID-19 illness, but any individual who has previously been infected with COVID-19 can experience it. Individuals who are not vaccinated against COVID-19 and become infected may have a higher risk of developing Long COVID compared to people who have been vaccinated. The CDC continues to study COVID-19 exposure to understand Long COVID to determine which individuals may be at a higher risk. (4)

Antibody Testing

An antibody test is a blood test that looks for antibodies which may determine if someone had a past infection or prior vaccination. Disease specific antibodies are proteins that help fight off infections and can provide protection against getting that disease again (immunity). Antibody tests are not to be used to diagnose a current infection, as it can take 1-3 weeks after infection for the body to develop antibodies. (5, 6) The 3 most used assays are enzyme-linked immunosorbent assays (ELISA), chemoluminescence assays (CLIA), and lateral flow assays (LFA). (7)

A positive antibody test for COVID-19 shows an individual may have antibodies from a previous infection with the virus or prior immunization. However, there is a chance the positive result means the antibodies are from an infection with a different virus from the same family of coronaviruses. There is also uncertainty as to the amount of protection the antibodies might provide, or how long that protection might last. In addition, an individual might also test positive even though they never had symptoms of COVID-19. Some people who are infected never develop antibodies. (8)

Regulatory Status

Based on a declaration by the Health and Human Services (HHS) Secretary in January 2020 that a public health emergency existed that could have a significant potential to affect national security or the health and security of United States citizens living abroad and involved the novel coronavirus (nCoV) that was first detected in Wuhan, China in 2019, the U.S. Food and Drug Administration (FDA) issued a guidance to provide a policy to help accelerate the availability of novel coronavirus (COVID-19) tests developed by laboratories and commercial manufacturers

for the duration of the public health emergency. That policy will remain in effect only for the duration of the public health emergency related to COVID-19. A revision was published on the FDA website in September 2022 and supersedes prior revisions. The FDA states “antibody tests are generally used to refer to tests that detect antibodies to the SARS-CoV-2 virus. Because the antibodies are part of the body’s immune response to exposure and not the virus itself, such testing cannot be used for diagnosis of acute infection." (9)

The FDA Guidance Document, “Emergency Use Authorization of Medical Products and Related Authorities” (updated January 2017), explains the FDA's general recommendations and procedures applicable to the authorization of the emergency use of certain medical products under sections 564, 564A, and 564B of the Federal Food, Drug, and Cosmetic Act as amended or added by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA). PAHPRA clarifies and enhances FDA’s authority to support emergency preparedness and response and foster the development and availability of medical products for use in the case of public health, military and domestic emergencies involving chemical, biological, radiological, and nuclear (CBRN) agents, including emerging infectious disease threats such as pandemic influenza. These medical products, also referred to as “medical countermeasures” or “MCMs,” include drugs (e.g., antivirals and antidotes), biological products (e.g., vaccines, blood products, and biological therapeutics), and devices (e.g., in vitro diagnostics and personal protective equipment). The emergency use authorization (EUA) authority under section 564 allows the FDA to facilitate availability and unapproved uses of MCMs needed to prepare for and respond to CBRN emergencies. The EUA authority is separate and distinct from use of a medical product under an investigational application (i.e., Investigational New Drug Application [IND] or Investigational Device Exemption [IDE]), section 561 expanded access authorities, and section 564A emergency use authorities discussed in section IV of the guidance. (10)

As a result of the public health emergency declaration, the FDA has approved a number of antibody tests under an EUA for use only during the public health emergency of COVID-19. A list of those EUA approved tests can be found on the FDA website. (10)

Rationale

This medical policy was developed in September 2020 and is based on a literature search as of January 27, 2024.

Antibody Detection Assays

Body fluid antibody detection is an effective strategy for the identification of coronavirus infection. A review published by Ji et al. (11) in July 2020 found that while nucleic acid and antibody detection assays play important roles in the rapid identification and isolation of COVID-19 patients to reduce further spread of SARS-CoV-2 infection, the current SARS-CoV-2 RNA detection assays have some limitations, including low detection sensitivity, long detection times, the need to extract RNA from clinical samples, the frequent false-negative nucleic acid results obtained in clinical applications, and the need to be performed by professional

technicians. Therefore, patients with low level of SARS-CoV-2 RNA are very likely be missed. With regards to SARS-CoV-2 RNA detection, more work is needed to achieve simple, highly effective release and enrichment of SARS-CoV-2 RNA from clinical samples for direct amplification.

Serologic tests are less likely to be reactive in the first several days to weeks of infection and they have a very limited utility for diagnosis in the acute setting. Detectable antibodies generally take several days to weeks to develop and the time to antibody detection varies by test. (2) In areas of low seroprevalence or low pre-test probability of infection, individual results should be interpreted with caution, since in this setting even serologic tests that have high specificity still have a low positive predictive value (i.e., a positive test may be as likely to reflect a false positive as a true positive). The serologic tests granted emergency use authorization by the FDA are binding antibody tests that detect SARS-CoV-2 antigens (nucleocapsid or spike protein) and include tests that can be performed at the point of care, as well as tests that require specialized equipment and trained laboratory personnel. The FDA has also granted emergency use authorization (EUA) for a test that detects neutralizing antibodies; although such tests are helpful to study the response to infection of vaccination, they do not offer a major diagnostic advantage over binding antibody tests since correlates of protection have not yet been established. The sensitivity and specificity of serologic tests are variable.

In 2022, UpToDate mentions a systematic review of 38 studies that evaluated the sensitivity of serologic testing by time since symptom onset in patients with COVID-19. They stated that IgM was detected in 23 percent by one week, in 58 percent by two weeks, and in 75 percent by three weeks; the corresponding detection rates for IgG were 30, 66, and 88 percent; while other studies have suggested that the rate of positive IgG approaches 100 percent by 16 to 20 days. (2) However, various serologic tests, including in-house laboratory-developed tests, were used in these studies, and their sensitivities within different time frames vary substantially. In particular, some lateral flow assays (which are used for point-of-care tests) are less sensitive than enzyme-linked immunosorbent assays or chemiluminescent immunoassays.

Specificity also varies by type of serologic assay. In contrast with IgG antibody and total antibody tests, IgM antibody, IgA antibody, and IgM/IgG differentiation tests generally have specificities below 99 percent. Cross-reactivity with other coronaviruses and other viral pathogens is a potential concern. (2) The duration of detectable antibodies is uncertain. In one study, IgG levels were noted to decline by a median of approximately 75 percent from the acute to early convalescent phase of illness, and at eight weeks following infection, 40 percent of asymptomatic patients and 13 percent of symptomatic patients did not have detectable IgG.

In 2022, the CDC (5) offered the following guidance specific to antibody testing for COVID-19:

- Antibody tests have public health value for monitoring and evaluating population levels of immunity, as well as clinical utility for patients. Antibody tests that have received Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) may be used for both public health and clinical purposes. Individual performance characteristics for each test can be found in the test's instructions for use (IFU).

- Antibody testing should not be used to determine whether someone is currently infected with SARS-CoV-2. Viral tests detect current infection.
- Antibody testing is not currently recommended to assess for immunity to SARS-CoV-2 following COVID-19 vaccination or to assess the need for vaccination in an unvaccinated person.
- Antibody testing does not replace virologic testing and should not be used to establish the presence or absence of acute SARS-CoV-2 infection.

In February 2022, the European Centre for Disease Prevention and Control (ECDC) published the first update for considerations for the use of antibody tests for SARS-Co-V2. Some key points include:

- At present, antibody tests are mostly used in research studies (mainly sero-epidemiological) at population level rather than for individual diagnosis of COVID-19 cases.
- A positive antibody test result can indicate a previous infection or vaccination but cannot be used to determine whether an individual is currently infectious or protected against infection.
- In the absence of a positive diagnostic test result, antibody tests cannot determine the time of infection.
- The antibody titres that correlate with protection from infection are currently unknown.
- There are a variety of antibody tests available, and it is extremely difficult to compare their results due to the diversity and lack of standardization.
- Antibody tests that target the spike protein are unable to distinguish between those who have been previously infected and those who have received at least one dose of a SARS-CoV-2 vaccine.
- There is a risk that the antibodies detected by the commercial tests currently in use will not prevent infection with newly emerging SARS-CoV-2 variants. (12)

On December 20, 2023, the National Institutes of Health updated their testing for SARS-CoV-2 infection which provides the following guidance specific to antibody testing (13):

- Antibody tests should not be used to diagnose current SARS-CoV-2 infection.
- Currently, antibody tests are not recommended for assessing SARS-CoV-2 immunity following COVID-19 vaccination or for assessing the need for vaccination in a person who is unvaccinated.
- Unlike nucleic acid amplification test (NAATs) and antigen tests, which detect the presence of SARS-CoV-2, serologic or antibody tests can detect recent or prior SARS-CoV-2 infection or vaccination. The CDC recommends that antibody tests should not be used to diagnose current SARS-CoV-2 infection. It may take 21 days or longer after symptom onset for seroconversion to occur (i.e., the development of detectable immunoglobulin M or immunoglobulin G antibodies to SARS-CoV-2).
- No serologic tests for SARS-CoV-2 have been approved by the FDA. Some, but not all, commercially available serologic tests for SARS-CoV-2 have received EUAs from the FDA.
- Antibody tests are not recommended for assessing SARS-CoV-2 immunity following COVID-19 vaccination or for assessing the need for vaccination in a person who is unvaccinated.

The FDA previously issued EUAs for more than 80 SARS-CoV-2 serologic tests since the beginning of the pandemic. However, these tests are not currently authorized for routine use in making individual medical decisions. SARS-CoV-2 serologic tests are authorized for detecting antibodies, but their ability to predict protective immunity has not been validated. Most of these tests are not standardized. Furthermore, as SARS-CoV-2 is not a well-conserved virus, mutations in the receptor binding domain of the virus could lead to decreased binding affinity between antibodies and SARS-CoV-2–specific antigens.

- If a serologic test is performed, the result should be interpreted with caution. It remains unclear how long SARS-CoV-2 antibodies persist following infection or vaccination. A negative serologic test result also does not preclude prior SARS-CoV-2 infection or vaccination against COVID-19. Some individuals who are infected with SARS-CoV-2 or who are vaccinated against COVID-19 (e.g., those who are immunocompromised) may not develop measurable levels of antibodies. It is presumed that those who do not have measurable antibodies after vaccination are at higher risk of SARS-CoV-2 infection than those who have measurable antibodies.

Professional Guidelines and Position Statements

Infectious Disease Society of America (IDSA)

The IDSA published practice guidelines (2023) regarding testing for COVID-19, which include the following recommendations for serologic (antibody) testing (14):

- The IDSA panel suggests against using serologic testing to diagnose SARS-CoV-2 infection during the first two weeks (14 days) following symptom onset (conditional recommendation, very low certainty of evidence).
- When SARS-CoV-2 infection requires laboratory confirmation for clinical or epidemiological purposes, the IDSA panel suggests testing for SARS-CoV-2 IgG or total antibody 3 to 4 weeks after symptom onset to detect evidence of past SARS-CoV-2 infection (conditional recommendation, very low certainty of evidence).
- When serology is being considered as an adjunct to NAAT for diagnosis, testing 3 to 4 weeks post-symptom onset maximizes the sensitivity and specificity to detect past infection.
- The IDSA panel makes no recommendation either for or against using IgM antibodies to detect evidence of past SARS-CoV-2 infection (conditional recommendation, very low certainty of evidence).
- The ISDA panel suggests against using IgA antibodies to detect evidence of past SARSCoV-2 infection (conditional recommendation, very low certainty of evidence).
- The IDSA panel suggests against using IgM or IgG antibody combination tests to detect evidence of past SARS-CoV-2 infection (conditional recommendation, very low certainty of evidence). IgM or IgG combination tests are those where detecting either antibody class is used to define a positive result.
- The IDSA panel suggests using IgG antibody to provide evidence of COVID-19 infection in symptomatic patients with a high clinical suspicion and repeatedly negative NAAT testing (weak recommendation, very low certainty of evidence). When serology is being

considered as an adjunct to NAAT for diagnosis, testing 3 to 4 weeks post-symptom onset maximizes the sensitivity and specificity to detect past infection.
- In pediatric patients with multisystem inflammatory syndrome, the IDSA panel suggests using both IgG antibody and NAAT to provide evidence of current or past COVID-19 infection (strong recommendation, very low certainty of evidence).

Summary of Evidence

There is limited evidence regarding the use of antibody testing for individuals infected with the SARS-CoV-2 (COVID-19) virus, other than those approved by the U.S. Food and Drug Administration under the Emergency Use Authorization during the declared public health emergency. As such, antibody testing for SARS-CoV-2 virus is considered experimental, investigational and/or unproven for all indications. Antibody testing for the SARS-CoV-2 (COVID-19) virus provided under an Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) during a public health emergency is **NOT** addressed by this policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	0224U, 0226U, 86328, 86408, 86409, 86413, 86769, 87426
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
04/01/2025	Reviewed. No changes.
03/15/2024	Document updated with literature review. Coverage unchanged. References 3, 4, 6-8, 13 and 14 were added; others updated, some removed.

03/15/2023	Reviewed. No changes.
08/15/2022	Document updated with literature review. Coverage unchanged. Reference 8 added; others updated.
01/01/2022	Reviewed. No changes.
01/01/2021	New medical document. Antibody testing for the SARS-CoV-2 (COVID-19) virus is considered experimental, investigational, and/or unproven for all indications. NOTE: Antibody testing for the SARS-CoV-2 (COVID-19) virus provided under an Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) during a public health emergency is not addressed by this policy.