Medical Coverage Policy

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COVID-19: In Vitro Diagnostic Testing

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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy

will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy discusses certain tests used to find the SARS-CoV-2 virus in the body. This virus causes COVID-19. Two types of tests help to diagnose COVID-19: molecular tests and antigen tests. Molecular tests look for the genetic material in the SARS-Co-V-2 virus while antigen tests look for the presence of small pieces of protein from the virus.

An antibody test, also called a serology test, is used to identify antibodies against the SARS-CoV-2 virus. Antibodies are proteins that work to fight infection in the body. An antibody test does not help diagnose COVID-19, but may be used for public health reasons, like to estimate how much of a virus is in a community and how quickly it may spread. It may also be used to plan where to offer testing.

This Policy applies to a test where results for one person are identified. It also discusses pooled sample testing, where test results for many people are reported together.

Nucleic acid pathogen testing by panels is outside the scope of this Coverage Policy. For information related to that type of testing, please review CP 0530 Nucleic Acid Pathogen Testing.

For the purpose of this Coverage Policy, molecular, antigen and antibody (serology) testing for the diagnosis of SARS-CoV-2 is informed by published statements by the FDA (2023), CDC (2024) and professional society recommendations (e.g., IDSA, 2024, 2023, 2022).

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Note: For information related to nucleic acid pathogen testing panels please review CP 0530 Nucleic Acid Pathogen Testing.

Medically Necessary

A molecular or antigen in vitro diagnostic test for SARS-CoV-2 (COVID-19) infection is considered medically necessary when ALL of the following criteria are met:

- clinical concern for a symptomatic COVID-19 infection
- ordered and administered by a licensed or authorized healthcare provider
- test is FDA approved or cleared or has an Emergency Use Authorization (EUA)
- performed by a CLIA-certified high or medium-complexity or CLIA-waived laboratory if so directed by test Instructions for Use

An antibody (serology) test for SARS-CoV-2 antibodies is considered medically necessary when the following criteria are met:

- ordered and administered by a licensed or authorized healthcare provider
- test is FDA approved or cleared or has an Emergency Use Authorization (EUA)
- performed by a CLIA-certified high or medium-complexity laboratory if so directed by test Instructions for Use

- results of a molecular or antigen test is non-diagnostic for COVID-19 and the results of the test will be used to aid in the diagnosis of a condition related to COVID-19 infection (e.g., Multisystem Inflammatory Syndrome [MIS], post-acute sequelae)

Not Covered or Reimbursable

Surrogate neutralization testing to determine the presence of SARS-CoV-2 antibodies is not covered or reimbursable.

An in vitro test to determine COVID-19 variants is not covered or reimbursable.

In vitro diagnostic testing (molecular, antigen, antibody) for COVID-19 infection is not covered or reimbursable for screening, including but not limited to BOTH of the following:

- asymptomatic individual, with or without exposure
- general population screening

An antibody (serology) test for SARS-CoV-2 antibodies is not covered or reimbursable for any other indication, not limited to the following:

- diagnose current or active infection
- determine need for COVID-19 vaccination
- assess immunity after COVID-19 vaccination

In vitro testing (i.e., molecular, antigen, antibody) is not covered or reimbursable for ANY of the following indications:

- purposes not primarily intended for individualized diagnosis or treatment of COVID-19
- testing done for employment purposes including testing conducted to screen for general workplace health and safety (such as employee "return to work" programs)
- determine prevalence of COVID-19 infection in the community
- public health surveillance for SARS-CoV-2
- public health screening
- screening assessment in a congregate setting (e.g., nursing home, correctional facility, school, residential dormitory)

A high-throughput molecular or antigen in vitro diagnostic test for the diagnosis of SARS-CoV-2 (COVID-19) infection is not covered or reimbursable unless billed by a CLIA-certified high-complexity laboratory.

If the above criteria are not met, in vitro testing (i.e., molecular, antigen, antibody) is not covered or reimbursable, including but not limited to the following indications listed below:

(Where applicable and appropriate, ICD-10 diagnosis codes that may be used to reflect population or public health screening scenarios have been included. This list is not all inclusive and may not represent an exact indication match.)

- testing conducted to screen for general workplace health and safety (e.g., return-to-work) (Z02.79)
- return-to-school (Z02.0)
- participation in sports (Z02.5)

- pre-employment (Z02.1)
- routine and/or executive physicals (Z02.89)
- travel
- recruitment to armed forces (Z02.3)
- insurance purposes (Z02.6)
- disability evaluation (Z02.71)
- encounter for administrative exam, unspecified (Z02.9)

***Please see Coding Table section for specific not covered or reimbursable ICD-10 code descriptions.**

An Over the Counter (OTC) test for SARS-CoV-2 (COVID-19) infection is not covered or reimbursable.

A test for SARS-CoV-2 (COVID-19) infection that is not diagnostic and/or does not otherwise meet the criteria above (e.g., Tiger Tech COVID Plus™) is not covered or reimbursable.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

An increasing body of evidence supports potential links between health disparity and social determinants of health as factors in rates of COVID-19 infection. According to the CDC (2023), some racial and ethnic groups are disproportionately affected by COVID-19. The CDC recognizes six key topic areas of social determinants of health that may increase risk of COVID-19 exposure, illness, hospitalization, long-term health and social consequences and death:

- social and community context
- healthcare access and use
- neighborhood and physical environment
- workplace conditions
- education
- income and wealth gaps

A COVID-19 Response Health Equity Strategy to outline a plan to reduce the disproportionate burden of COVID-19 among racial and minority populations has been developed by the CDC (2023).

General Background

COVID-19 is the infectious disease caused by the coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus is highly contagious and is believed to be spread from person to person through respiratory droplets or when aerosol is produced as an infected person coughs or sneezes. An infected individual may be asymptomatic or exhibit a variety of symptoms.

Common symptoms of COVID-19 infection are fever, chills, cough and shortness of breath, fatigue, body aches or muscle pain, headache, congestion or runny nose, sore throat, new loss of taste or smell, nausea, vomiting and diarrhea (Centers for Disease Control and Prevention [CDC], 2024; Infectious Disease Society of America [IDSA], 2022). These symptoms typically appear 2–14 days after exposure. Symptoms can progress rapidly to severe respiratory distress requiring hospitalization, culminating in death. Emergency warning signs for Covid-19 include persistent pain or pressure in chest, new confusion, inability to wake or stay awake, and pale, gray, or blue-colored skin, lips, or nail beds (CDC, 2024).

Prevalence: Prevalence of disease is a measure of risk and is the proportion of persons in a population who have a particular disease or attribute at a specified point in time or over a specified period of time. It is used to characterize the occurrence of health events in a population and as a measure of public health impact of disease (CDC, 2023). Positive and negative predictive values of a test are affected by prevalence. In a high-prevalence setting, the positive predictive value increases (i.e., more likely that persons who test positive are truly positive). When a test is used in a population with low prevalence the positive predictive value is decreased (i.e., there are more false positives). Likewise, negative predictive value is also affected by prevalence. In a high-prevalence setting, the negative predictive value declines whereas in a low-prevalence setting, it increases (CDC, 2022).

At this time there is no national reference standard for the prevalence rate of COVID-19; rather, it is based on complex mathematical modeling. The CDC notes that prevalence of SARS-CoV-2 antibody in the US is expected to be low, ranging from <5% to 25%, so that testing might result in relatively more false-positive results and fewer false negative results (2022).

Testing: For the purpose of this Coverage Policy, molecular, antigen and antibody (serology) testing for the diagnosis of SARS-CoV-2 is informed by authoritative statements by the FDA (2023), CDC (2024) and published professional society recommendations (e.g., IDSA, 2024, 2023, 2022). Specimen sources used for in vitro diagnostic devices are taken from the human body, such as swabs of mucus from inside the nose or back of the throat, sputum, saliva, or blood taken from a vein or finger stick.

Two types of tests are used to diagnose a current COVID-19 infection: polymerase Chain Reaction (PCR) tests (a type of molecular nucleic acid amplification test [NAAT]) and antigen tests. These tests detect parts of the SARS-CoV-2 virus and can be used to diagnose infection with the SARS-CoV-2 virus. Molecular tests are not useful in distinguishing between highly infective viruses versus ones that have been neutralized by the host, and it cannot assess immunity status against SARS-CoV-2 antibody. Antibody (serology) tests cannot be used to diagnose a current infection (CDC, 2024; FDA, 2023).

Any laboratory or testing site that performs diagnostic or screening testing must have a Clinical Laboratory Improvement Amendments (CLIA) certificate and meet all applicable CLIA requirements. Tests for SARS-CoV-2 (COVID-19 infection) must be approved or cleared by the U.S. Food and Drug Administration (FDA) or have received an Emergency Use Authorization from the FDA.

Regarding a testing strategy for COVID-19 diagnostic testing and screening, the CDC (2024) notes the following:

Diagnostic Testing: Diagnostic testing is intended to identify current infection in individuals and should be performed on anyone that has signs and symptoms consistent with COVID-19 and/or following recent known or suspected exposure to SARS-CoV-2. Examples of diagnostic testing include:

- testing individuals with signs or symptoms consistent with COVID-19
- testing individuals who were exposed to someone with a confirmed or suspected case of COVID-19

Screening: A screening test is one that is performed on an individual who is asymptomatic; that is, has no symptoms of disease. Guidance from the CDC (2024) notes screening helps to identify unknown cases so that measures can be taken to prevent further transmission.

Regarding screening testing as a prevention strategy, the CDC notes screening:
- may be incorporated as part of a comprehensive approach to reducing transmission.
- may be most valuable in specific settings where early identification is essential to reducing transmission and mitigating risk for severe disease among populations at high risk.
- point-in-time screening testing is screening testing that happens on a situational basis to screen a person, or group of people, for COVID-19 at a single time point.
- serial screening testing is screening testing that is repeated at different points in time within a group, such as testing every 3 days for everyone in a particular setting or facility.
- can improve detection of SARS-CoV-2.

Examples of screening include testing of all of the following:
- employees in a workplace setting
- students, faculty, and staff in a school setting
- a person before or after travel

The CDC (2024) and FDA (2022) published guidance regarding when an individual should be tested:
- "If you have symptoms, test immediately.
    - If you are only going to take a single test, a PCR test will provide a more reliable negative test result.
    - If you use an antigen test, a positive result is reliable, but a negative test is not always accurate.
    - If your antigen test is negative, take another antigen test after 48 hours or take a PCR test as soon as you can.
- If you were exposed to COVID-19 and do not have symptoms, wait at least five full days after your exposure before testing. If you test too early, you may be more likely to get an inaccurate result.
    - If you are only going to take a single test, a PCR test will provide a more reliable negative test result.
    - If you use an antigen test, a positive result is reliable, but a negative test is not always accurate.
    - If your antigen test is negative, take another antigen test after 48 hours or take a PCR test as soon as you can.
    - If your second antigen test is also negative, wait another 48 hours and test a third time.
- If you are in certain high-risk settings, you may need to test as part of a screening testing program.
- Consider testing before contact with someone at high risk for severe COVID-19, especially if you are in an area with a medium or high COVID-19 Community Level.
- An individual who has tested positive for COVID-19 using a nucleic acid amplification test (NAAT) within the past 90 days should not use a NAAT for repeat testing.

Screening testing can provide early identification and isolation of people with COVID-19 who do not have symptoms and may be unknowingly transmitting SARS-CoV-2. Screening testing may be most valuable in specific settings where early identification is essential to reducing transmission

and mitigating risk for severe disease among populations at high risk. This is especially important when community risk or transmission levels are substantial or high. A person's vaccination status does not affect the results of their viral test for SARS-CoV-2 (CDC, 2024).

Regarding use of at-home antigen tests, the FDA (2022) notes the following testing guidance:

- when initial test result is negative, repeat testing is recommended whether or not you have COVID-19 symptoms
- if you receive a positive result initially or after a repeat test, this means the test detected the SARS-CoV-2 virus and you most likely have COVID-19.
- if you receive a negative result, the test did not detect the SARS-CoV-2 virus at the time of that test.
    - if you have COVID-19 symptoms test again 48 hours after the first negative test, for a total of at least two tests. If the second is negative and there is still concern for Covid-19, you may choose to test again 48 hours after the second test, consider getting a laboratory-based molecular COVID-19 test or call your health care provider.
    - if you do not have COVID-19 symptoms and were exposed, test again after 48 hours after the first negative test, and again 48 hours after the second negative test, for a total of three tests. If the third test is negative and there is still concern for Covid-19, you may choose to test again using an antigen test, consider getting a laboratory-based molecular COVID-19 test or call your health care provider.
    - If you get a positive result on any repeat test with an at-home COVID-19 antigen test, you most likely have COVID-19 and should follow the CDC guidance for people with COVID-19.

Public Health Surveillance: Public health surveillance is the ongoing, systematic collection, analysis and interpretation of health-related data performed to plan, implement, and evaluate public health policy and practice. Surveillance testing is intended to monitor community- or population-level outbreaks of disease and to characterize the incidence and presence of disease. This testing is performed on de-identified specimens. Results are not linked to individuals; therefore, they cannot be used for individual health decisions. Tests used for SARS-CoV-2 surveillance do not meet FDA or CLIA requirements for diagnostic or screening testing (CDC, 2024).

Limitations to Testing: Diagnostic testing errors can result in false positives and/or false negatives that stem from improper sample collection, testing procedural errors, and variability in assay performance (sensitivity/specificity). The performance of tests is described by their analytical and clinical sensitivity, specificity, and positive and negative predictive values. Analytical sensitivity is the assay's ability to detect the minimum concentration of a substance in a sample while clinical sensitivity measures how accurately a test identifies positive patients who are infected. Analytical specificity refers to the ability to detect only the desired analyte in a specimen without cross reacting with other substances, while clinical specificity determines how accurately a test identifies negative patients who do not have COVID-19. A test with lower sensitivity test means higher false negative results, while lower specificity means higher false positive results. A test with good analytical sensitivity and specificity does not necessarily correlate with clinical sensitivity and specificity (Chau et al., 2020). Regarding antibody (serology) testing positive predictive and negative values describe how likely it is that a person who receives a positive result from a test truly does have antibodies to SARS-CoV-2 and how likely it is that a person who receives a negative result from a test truly does not have antibodies to SARS-CoV-2 (FDA, 2023). Multiple methods are used in formation and processing of molecular, antigen and serology tests. Surveillance monitors population-level burden of disease or to characterize the incidence and prevalence of disease. Surveillance testing results are not linked to individual people; and therefore, cannot be used for individual healthcare decision-making or individual public health

actions (CDC, 2024). The FDA has established minimum validation standards for these tests, which are authorized under the Emergency Use Authorization (EUA) designation.

Molecular Testing: Molecular tests using nucleic acid amplification methodologies are most commonly used to determine the presence or absence of SARS-CoV-2 virus and to make a diagnosis of active infection. Nucleic acid amplification tests (NAAT) such as reverse transcription-polymerase chain reaction (RT-PCR) tests, remain the "gold standard" for clinical diagnostic detection of SARS-CoV-2 (National Institutes of Health [NIH], 2023). Molecular testing involves the in vitro qualitative detection of ribonucleic acid (RNA) from the SARS-CoV-2 virus. Analytical validity of the test is highly accurate in controlled laboratory conditions. These tests can identify and quantify the presence of infectious agents in a sample through the process of detection, amplification, and output measurement.

Understanding the predictive value of molecular testing with regards to time from exposure and symptom onset is important as the assay may not have been appropriately validated against a clinically meaningful reference standard for detecting SARS-CoV-2 in the absence of symptoms, such as during earlier stages of the disease, or in asymptomatic individuals (Chau et al., 2020). Nonbinding standards from the FDA for validation of tests recommend analytical sensitivity (limit of detection [LOD]) for the virus of 95%. The LOD is defined as the lowest concentration where at least 19 of 20 viral replicates are positive.

Most test developers self-report high performance statistics with their FDA submissions, with reported results ranging from 95-100%. Results may not be as robust as accuracy is dependent on when in the course of illness, the sample is collected, test performance, collection technique and quality, storage and transport conditions. As an example, if the test has a 95% accuracy in its performance in the lab in detecting the virus, 50,000 individuals would be incorrectly identified as having a negative result in a sample of 1,000,000 test results. The test cannot distinguish between active virus and dead viral fragments, which may result in an incorrect diagnostic interpretation of a positive result.

The FDA notes that clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status. Positive results do not rule out bacterial infection or co-infection with other viruses. The agent detected may not be the definite cause of disease. Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information (2022).

Sensitivity, specificity, and positive and negative predictive values for each test for which an FDA EUA has been granted are reported in the individual test EUA summary or Instructions for Use and can be accessed on the FDA website at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covid19euas.

The ISDA (2023) published guidelines regarding molecular testing for COVID-19 infection, including the following:

- SARS-CoV-2 nucleic acid amplification test (NAAT) is recommended in symptomatic individuals in the community suspected of having COVID-19.
- For symptomatic individuals suspected of having COVID-19, the IDSA panel suggests collecting and testing swab specimens from either the nasopharynx (NP), anterior nares (AN), oropharynx (OP), or midturbinate regions (MT); saliva, or mouth gargle.

- The IDSA panel suggests that for symptomatic individuals suspected of having COVID-19, AN and MT swab specimens may be collected for SARS-CoV-2 RNA testing by either patients or healthcare providers.
- The IDSA panel suggests using either rapid or standard laboratory-based NAATs in symptomatic individuals suspected of having COVID-19.
- A single SARS-CoV2 viral RNA test is suggested in symptomatic or asymptomatic individuals suspected of having COVID-19 whose initial NAAT result is negative. Repeated testing is not suggested for this population.
- For individuals who have clinical or epidemiologic reasons that might make testing desirable, SARS-CoV-2 RNA testing is recommended in asymptomatic individuals who are either known or suspected to have been exposed to COVID-19. Known exposure is defined as direct contact with a laboratory confirmed case of COVID-19. Suspected exposure was defined as working or residing in a congregate setting (e.g., long-term care, correctional facility, cruise ship, factory, among others) experiencing a COVID-19 outbreak.
- For individuals who have clinical or epidemiologic reasons that might make testing desirable, the IDSA panel suggests using either rapid or laboratory-based NAATs in asymptomatic individuals with known exposure to SARS-CoV-2 infection.
- SARS-CoV-2 RNA testing is not recommended in an asymptomatic individual with no known contact with COVID-19 who are being hospitalized.
- The IDSA panel suggests against routine SARS-CoV-2 NAAT of asymptomatic individuals without a known exposure to COVID-19 who are undergoing a medical or surgical procedure.
- The IDSA panel suggests against routinely repeating NAAT before medical or surgical procedures in patients with a recent history of COVID-19.
- The IDSA panel suggests against routinely repeating NAAT in patients with COVID-19 to guide release from isolation.
- The Panel makes no recommendations for or against SARS-CoV-2 RNA testing before initiating immunosuppressive therapy in an asymptomatic individual with cancer

Pooled Sample Diagnostic Testing: Pooled sample testing for the qualitative detection of nucleic acid from the SARS-CoV-2 virus has been proposed as a laboratory method to conserve testing resources. The technique allows upper or lower respiratory samples from several individuals (e.g., 4-5 test samples) to be combined and tested together in a batch. This method may be useful for diagnostic testing in a population where low prevalence of infection is present. Use in a population with high-prevalence of COVID-19 infection would likely result in the need to perform individual testing to identify the positive sample(s) and result in the consumption of additional testing resources.

There are limitations to pooled testing. In a pooling procedure, the laboratory cannot ensure the diagnostic integrity of an individual specimen because it is combined with other specimens before testing. Specimen integrity can also be affected by the quality of swab specimen collection, which can result in some swabs having limited amounts of viral genetic material for detection. Inadequate individual specimens might not be eliminated from the pooled specimen before testing (CDC, 2021). A decrease in performance is also likely with pooling strategies due to dilution of the primary clinical sample and a decrease in sensitivity may result.

The FDA notes that because samples are diluted there is a greater likelihood of false negative results, particularly if the test is not properly validated (2020). In general, the larger the pool of specimens, the higher the likelihood of generating false negative results (CDC, 2021). These limitations mean that monitoring the prevalence of disease and properly validating the assay for the real-world population in which the test is being used is important to limit the potential for false negative results. Negative results from pooled samples should be considered to be presumptive negatives.

Although proposed as a method that consumes fewer testing resources, a unique sample collection kit, swab and reagents must be used for each specimen collection regardless of pooling technique used. If the sample is collected by someone other than the individual being tested, personal protective equipment is also required. If the pooled sample is negative, it can be deduced that all individuals tested within the pool have a negative test result and the pooled test result is sufficient. However, if the pooled sample is inconclusive or positive, each sample must be tested individually to determine which sample or samples are positive, resulting in the use of additional testing resources.

Antigen Testing: An antigen test is an immunoassay test that detects the presence of a specific viral antigen. The antigen is generally detectable during the acute phase of infection; however, an antigen test may not detect all active infections. Positive results indicate the presence of viral antigens. Samples are collected from areas such as the nasal passage.

Antigen testing is subject to the same analytic and clinical performance limitations, such as those described for molecular tests. An antigen test generally has similar specificity as a molecular test but are less sensitive than NAATs and may yield false negatives if the viral protein production is low or if there is not enough virus replication in the sampled area. FDA EUA-designated antigen assays report a clinical sensitivity of 80% when compared to an EUA-designated molecular device. Test specificity of 100% is reported. Negative results do not rule out COVID-19. Antigen tests are available for at-home (self) testing, at point of care or in the laboratory.

Antigen tests should not be used as the sole basis for treatment or for patient management decisions and should be treated as presumptive and confirmed with a molecular assay if necessary. The analytic sensitivity, specificity and positive and negative predictive values of individual tests that have received an FDA EUA designation can also be accessed on the FDA website at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covid19euas. Because of the performance characteristics (e.g., sensitivity, specificity) of some antigen tests, it may be necessary to confirm some test results such as a negative test in persons with symptoms or a positive test in an individual without symptoms. The CDC has developed an Antigen Testing Algorithm to be used when confirmatory testing is needed (CDC, 2023).

An advantage of antigen testing is that the methodology lends itself to the point of care testing environment and results can be delivered fairly rapidly, often within minutes. While the main advantage of these antigen tests is the speed of the test, they are often plagued with inaccurate results and have lower sensitivity and specificity than nucleic acid assays Clinical correlation with patient history and other diagnostic information is necessary to determine infection status (Chau et al., 2020).

Regarding antigen tests, the CDC (2023) notes the following:

- In a symptomatic individual, infection with SARS-CoV-2 can be identified by the presence of a positive antigen test.
- A negative antigen test result for a symptomatic person should be confirmed with an FDA-authorized NAAT. CDC recommends using a NAAT that has been evaluated against the FDA reference panel for analytical sensitivity. If the person has a low likelihood of SARS-CoV-2 infection (e.g., no known exposure), clinical judgement should be used to determine whether a confirmatory NAAT should be performed.
- Because antigen tests perform best in symptomatic people and within a certain number of days since symptom onset, antigen tests are used frequently on people who are

symptomatic. Antigen tests also may be informative in diagnostic testing situations in which the asymptomatic person has a known exposure to a person with COVID-19.
- Antigen tests have been used for screening testing in high-risk congregate housing settings, such as nursing homes, in which repeat testing has quickly identified people with COVID-19, informing infection prevention and control measures, thus preventing transmission.

Serology (Antibody) Testing: Clinical utility for diagnosis using antibody testing has not been established; the relationship between the presence of antibodies and re-infection and or re-activation of the virus is unknown. Antibody testing may be used as an aid in diagnosis but is of limited value when COVID-19 infection is suspected because such testing cannot be used to rule in or rule out an active infection. Likewise, a positive test does not necessarily assure immunity.

Serologic testing by itself should not be used to establish the presence or absence of SARS-CoV-2 infection or reinfection. Such testing is not recommended as a tool to establish or diagnose SARS-CoV-2 infection (FDA, 2022; CDC, 2023; National Institutes of Health [NIH], 2023). At this time, no antibody (serology) test has been validated to establish or diagnose SARS-CoV-2 infection or authorized by the FDA for diagnostic purposes (FDA, 2022; CDC, 2023).

Antibody (or serology) tests are used to test for the presence of antibodies from previous infection or vaccination and can aid in fulfilling the case definition for multisystem inflammatory syndrome in children (MIS-C) and adults (MIS-A). Serology tests play a role in the fight against COVID-19 by helping health care professionals identify individuals who may have developed an adaptive immune response to SARS-CoV-2 (CDC, 2023; FDA, 2022). The primary role for antibody testing is to inform on exposure to a specific pathogen by detection of the presence of antibodies to a specific virus. However, antibodies may not be present among those tested early in illness or among those who never develop detectable antibodies following infection. In addition, the presence of antibodies may reflect previous infection and may be unrelated to the current illness.

In humans, three types of antibodies or immunoglobulins have been the target of COVID-19 serological tests: IgM, IgG, and IgA. Although the dynamics of the immune response in COVID-19 are not fully understood, typically IgM antibodies are produced by host immune cells during the early stages of a viral infection. IgG is often the most abundant antibody in the blood and plays a more prominent role in the later stages of infection and in establishing long-term immune memory. Recent studies show that IgA, predominately present in the mucosal tissue, may also play a critical role in immune response and disease progression (Ghafferi et al., 2020). Antibodies to SARS-CoV-2 are generally detectable in blood several days after initial infection, although the duration of time that antibodies are present post-infection is not well characterized (FDA, 2022). Asymptomatic patients may seroconvert later in the course of infection or may not at all (Chau et al. 2020).

The FDA notes that a positive antibody test result is difficult to interpret for a number of reasons. For some assays both sensitivity and specificity are poor or undefined in a real-world population. Accuracy of an antibody test depends in part on the prevalence of the infection in the population. The prevalence of SARS-CoV-2 antibody positive individuals in the U.S. population is currently unknown. Prevalence may vary based on the duration of the virus, the effectiveness of mitigations and between locations and different groups of people, due to different rates of infection. In low prevalence populations, such as much of the asymptomatic general population, the result of a single antibody test is not likely to be sufficiently accurate to make an informed decision regarding whether or not an individual has had a prior infection or truly has antibodies to the virus (2022). A second test, typically one assessing for the presence of antibodies to a different viral protein, generally would be needed to increase the accuracy of the overall testing results (FDA, 2022). As a result, the clinical utility of serology testing is uncertain.

The positive and negative predictive values describe how likely it is that a person who receives a positive result from a test truly does have antibodies to SARS-CoV-2 and how likely it is that a person who receives a negative result from a test truly does not have antibodies to SARS-CoV-2. Different serological tests have varying levels of specificity and sensitivity. Sensitivity of antibody tests for SARS-CoV-2 are typically reported to be between 88-100%, specificity 94-100% and positive and negative predictive value at 5% prevalence: 50.4-100% and 99.4-100%, respectively. This means that a positive result may result in an incorrect finding in as much as 50% of the time if the prevalence of the disease in the general population is 5%. False positives can result from cross-reactivity with pre-existing antibodies from previous infections such as other coronaviruses that cause the common cold; SARS-CoV or MERS-CoV. Negative results may result because antibodies have not yet formed during the early stages of infections (Chau et al., 2020)

Studies are underway to better inform the appropriate use of these tests, such as which antibodies may indicate a level of protection that would prevent or reduce the severity of infection or re-infection as well as the duration for which this protection may last. Large-scale validation studies on the performance of these assays are critical before they can be used in seroprevalence studies for disease surveillance. A collaborative effort by the FDA, National Institutes of Health, CDC and Biomedical Advanced Research and Development Authority (BARDA) is currently underway to conduct performance assessments and establish the validity of serological tests against a well-characterized set of clinical samples collected before and during the pandemic and correlate them with neutralization assays (Chau et al., 2020).

Antibody tests that have received an FDA EUA designation are designed to detect IgA, IgM or IgG antibodies alone or a combination of some or all antibodies reported as a total result. Currently, there is no substantive performance advantage of assays whether they test for IgG, IgM and IgG, or total antibody. Thus, immunoglobulin class should not determine the assay chosen in most circumstances (CDC, 2022).

Serologic testing should not be used to determine immune status in individuals until the presence, durability, and duration of immunity are established. Serologic testing can be offered as a method to support diagnosis of acute COVID-19 illness for persons who present late. For persons who present 9–14 days after illness onset, serologic testing can be offered in addition to recommended viral direct detection methods such as polymerase chain reaction or antigen detection tests. However, serologic testing should be offered as a method to help support a diagnosis when patients present with late complications of COVID-19 illness, such as multisystem inflammatory syndrome in children (MIS-C) and in adults (MIS-A) (CDC, 2023).

The results of ongoing research are needed before it is known whether antibodies are associated with protection from future infection. When used for surveillance, the results can help determine how widely the virus has spread in communities. Results from tests used for surveillance only are generally not shared with individual patients.

Regarding antibody (serology) testing, the CDC (2022) notes:

- Antibody tests can be used to:
    - Determine if a person has COVID-19 antibodies, which suggests past infection or vaccination.*
    - Aid in the diagnosis of multisystem inflammatory syndrome in children (MIS-C) and in adults (MIS-A).
    - Monitor and evaluate population levels of immunity

- Antibody tests should not be used to:

- Diagnose current infection.**
- Determine if someone can return to work or school.
- Group people together in settings such as schools, dormitories, and correctional facilities; or to exempt someone from screening testing.
- Exempt a person who wears personal protective equipment (PPE) at work from following site-specific requirements

**Acute infection from SARS-CoV-2 is determined best by diagnostic testing using a nucleic acid amplification test (NAAT) or antigen test.

The CDC (2022) also notes:

- Persons suspected of having COVID-19 who test positive by direct viral detection methods for SARS-CoV-2 (e.g., NAAT or antigen detection tests) typically begin to develop measurable antibody 7–14 days after illness onset, and by 3 weeks most persons will test positive for antibody. During this interval, the sensitivity of detecting infection using NAAT or antigen detection testing decreases and the sensitivity of serologic testing increases.
- Antibody testing may be useful to support the diagnosis of COVID-19 illness or complications of COVID-19 in the following situations:

    - A positive antibody test at least 7 days following acute illness onset in persons who had a previous negative antibody test (e.g., seroconversion) but did not receive a positive viral test might indicate SARS-CoV-2 infection between the dates of the negative and positive antibody tests.
        - A positive antibody test can help support a diagnosis when patients present with complications of COVID-19, such as multisystem inflammatory syndrome or other post-acute sequelae of COVID-19.
        - Antibody testing can be used for clinical and public health purposes to help differentiate antibodies produced due to past infection from those produced by vaccination by using tests that measure antibodies against different protein targets.
        - Antibody testing is currently not recommended to assess for immunity to SARS-CoV-2 following COCID-19 vaccination.

The CDC notes that although the surrogate neutralization test exhibits correlation to a plaque reduction neutralization test, the clinical or public health applicability has not been established for this test.

Although current FDA EUA indications do not preclude the use of these tests in vaccinated individuals, none of the currently authorized tests have been specifically authorized to assess immunity or protection of people who have received a COVID-19 vaccine, including people with immunocompromising conditions.

Whether the test has been validated to specifically detect antibodies against the antigens employed by the test and whether the antigens cross-react with antibodies to antigens that are not employed by the test should be considered.

Antibody (serology) tests that have received an FDA EUA designation can be found at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#sarscov2antibody.

Multisymptom Inflammatory Syndrome (MIS): MIS is a rare but serious condition associated with COVID-19 in which different body parts become inflamed, including the heart, lungs, kidneys,

brain, skin, eyes, or gastrointestinal tract (CDC, 2023). This rare syndrome shares common features with other inflammatory conditions such as Kawasaki disease, acute viral infection myocarditis (e.g., influenza, enteroviruses), rickettsial disease (e.g., typhus), staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis, and macrophage activation syndromes. MIS-C case definition includes individuals younger than 21 years old, and MIS-A case definition includes individuals 21 years and older. Signs and symptoms of MIS include an ongoing fever plus one of the following: stomach pain, bloodshot eyes, diarrhea, dizziness, or lightheadedness (signs of low blood pressure), skin rash or vomiting.

In an individual with suspected MIS-C a molecular test may be positive or negative for the SARS-CoV-2 virus. While not diagnostic of infection with SARS-CoV-2 infection, an antibody (serology) test may be considered appropriate in a symptomatic individual to aid in the diagnosis of MIS-C when results of molecular or antigen tests are non-diagnostic for COVID-19 infection. As a result of the variable performance of serology tests described in the above antibody testing section, the clinical utility of the antibody result must be interpreted in the context of the individual's treatment history and presenting symptom complex.

Several professional societies, including the American Academy of Pediatrics, the American College of Rheumatology and the Royal College of Paediatrics and Child Health (2020) and the CDC (2023) have developed a case definition for MIS in adults (MIS-A) and children (MIS-C)
The CDC Case Definition for Multisystem Inflammatory Syndrome in Adults (MIS-A) was developed in 2021 through expert opinion and is intended to assist in identification and reporting of MIS-A cases to CDC passive surveillance (CDC, 2023):

Adults (MIS-A)

- General Criteria
  - An individual ≥21 years hospitalized for ≥24hours, or with an illness resulting in death, who meets the following clinical and laboratory criteria. The individual should not have a more likely alternate diagnosis for the illness (e.g., bacterial sepsis, exacerbation of a chronic medical condition).
- Clinical Criteria
  - Subjective fever or documented fever (≥38.0C) for ≥24 hours prior to hospitalization or within the first three days of hospitalization AND at least three of the following clinical criteria occurring prior to hospitalization or within the first three days of hospitalization. At least one must be a primary clinical criterion.
    - Primary Clinical Criteria
      - severe cardiac illness includes myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF<50%), 2nd/3rd degree A-V block, or ventricular tachycardia. (Note: cardiac arrest alone does not meet this criterion)
      - rash and non-purulent conjunctivitis
    - Secondary Clinical Criteria
      - new onset neurologic signs and symptoms includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome)
      - shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy)
      - abdominal pain, vomiting, or diarrhea
      - thrombocytopenia (platelet count <150,000/microliter
- Laboratory Evidence
  - Presence of laboratory evidence of inflammation and SARS-Co-V2 infection
  - Elevated levels of at least two of the following
    - C-reactive protein

    - Ferritin
    - IL-6
    - Erythrocyte sedimentation rate
    - Procalcitonin
  - A positive SARS-Co-V2 test for current or recent infection by RT-PCR, serology, or antigen detection

The Council of State and Territorial Epidemiologists (CSTE) and CDC have developed a standardized surveillance case definition for multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection, effective January 1, 2023 (CDC, 2023):

Children (MIS-C): Any individual aged <21 years that's meets certain clinical AND laboratory criteria, OR clinical and epidemiologic criteria OR vital records criteria:

Clinical criteria

- An illness characterized by <u>all of the following</u>, in the absence of a more likely alternative diagnosis*
  - Subjective or documented fever (temperature ≥38.0º C)
  - Clinical severity requiring hospitalization or resulting in death
  - Evidence of systemic inflammation indicated by C-reactive protein ≥3.0 mg/dL (30 mg/L)
  - New onset manifestations in <u>at least two</u> of the following categories:
    - Cardiac involvement indicated by:
      - Left ventricular ejection fraction <55% OR
      - Coronary artery dilatation, aneurysm, or ectasia, OR
      - Troponin elevated above laboratory normal range, or indicated as elevated in a clinical note
    - Mucocutaneous involvement indicated by:
      - Rash, OR
      - Inflammation of the oral mucosa (e.g., mucosal erythema or swelling, drying or fissuring of the lips, strawberry tongue), OR
      - Conjunctivitis or conjunctival injection (redness of the eyes), OR
      - Extremity findings (e.g., erythema [redness] or edema [swelling] of the hands or feet)
    - Shock**
    - Gastrointestinal involvement indicated by:
      - Abdominal pain, OR
      - Vomiting, OR
      - Diarrhea
    - Hematologic involvement indicated by:
      - Platelet count <150,000 cells/μL, OR
      - Absolute lymphocyte count (ALC) <1,000 cells/μL

Laboratory criteria:

- Detection of SARS-CoV-2 RNA in a clinical specimen*** up to 60 days prior to or during hospitalization, or in a post-mortem specimen using a diagnostic molecular amplification test (e.g., polymerase chain reaction [PCR]), OR
- Detection of SARS-CoV-2 specific antigen in a clinical specimen*** up to 60 days prior to or during hospitalization, or in a post-mortem specimen, OR
- Detection of SARS-CoV-2 specific antibodies^ in serum, plasma, or whole blood associated with current illness resulting in or during hospitalization

Epidemiologic Linkage criteria:

- Close contact‡ with a confirmed or probable case of COVID-19 disease in the 60 days prior to hospitalization

Vital Records criteria:

- person whose death certificate lists MIS-C or multisystem inflammatory syndrome as an underlying cause of death or a significant condition contributing to death

*If documented by the clinical treatment team, a final diagnosis of Kawasaki Disease should be considered an alternative diagnosis. These cases should not be reported to national MIS-C surveillance.
**Clinician documentation of shock meets this criterion.
***Positive molecular or antigen results from self-administered testing using over-the-counter test kits meet laboratory criteria.
^Includes a positive serology test regardless of COVID-19 vaccination status. Detection of anti-nucleocapsid antibody is indicative of SARS-CoV-2 infection, while anti-spike protein antibody may be induced either by COVID-19 vaccination or by SARS-CoV-2 infection.
‡Close contact is generally defined as being within 6 feet for at least 15 minutes (cumulative over a 24-hour period). However, it depends on the exposure level and setting; for example, in the setting of an aerosol-generating procedure in healthcare settings without proper personal protective equipment (PPE), this may be defined as any duration.

In Vitro Testing for Population or Public Health Screening: Molecular, antigen and antibody (serology) testing has been proposed to determine prevalence of COVID-19 infection in a population. Testing strategies include screening and surveillance. Similar analytic and clinical performance limitations as described above apply to testing for population and public health screening; these tests have not been validated for use in the asymptomatic population.

Screening for COVID-19 is looking for occurrence at the individual level even if there is no individual reason to suspect infection, such as a known exposure. This includes broad screening of asymptomatic individuals without known exposure with the intent of making individual decisions based on the test results.

Screening tests are intended to identify infected individuals prior to development of symptoms or those infected individuals without signs or symptoms who may be contagious, so that measures can be taken to prevent those individuals from infecting others. Examples of screening include testing plans developed by a workplace to test all employees returning to the workplace, plans developed by a school to test all students and faculty returning to the school, testing requirements before participation in sports, pre-employment physicals and testing of residents and employees in congregate setting such as nursing homes, assisted living and dormitory residences. Testing is performed regardless of exposure or signs and symptoms, with the intent of using those results to determine who may return or what protective measures to take on an individual basis. (FDA, 2022).

Surveillance for COVID-19 is not regulated by the FDA. An example of such testing may be a plan developed by a State Public Health Department to randomly select and sample 1% of all individuals in a city on a rolling basis to determine local infection rates and trends. It is generally used to monitor for an occurrence, such as an infectious disease outbreak in a population or community, or to characterize the occurrence once detected, such as looking at the incidence and prevalence of the occurrence. Surveillance testing is primarily used to gain information at a population level, rather than an individual level. Surveillance testing may be random sampling of a certain percentage of a specific population to monitor for increasing or decreasing prevalence and determining the population effect from community interventions such as social distancing (FDA, 2022).

In vitro testing for the purpose of population or public health screening, including to determine prevalence of COVID-19 infection in the community or congregate setting is not necessary to diagnose the infection caused by SARS-COV-2 virus. Likewise, screening for other viral diseases

does not diagnose COVID-19 infection. Testing for any of the following is not a covered benefit under most Cigna standard benefit plans.

- return-to-work
- return-to-school
- participation in sports
- pre-employment
- routine and/or executive physicals
- travel
- recruitment to armed forces
- insurance purposes
- disability evaluation
- encounter for administrative exam, unspecified

Other Non-Diagnostic Tests and Devices: FDA EUA status has been granted for additional tests and devices that are not considered diagnostic for SARS-CoV-2 (COVID-19) infection. They may be used for population and public health screening and surveillance purposes.

Testing for variants of SARS-CoV-2 is another type of testing used for surveillance. The CDC works with public health officials to monitor and track all variants. According to the CDC (2024) viral genomic sequencing is used to identify, track, and monitor COVID-19 variants to protect the public's health. The CDC's COVID Data Tracker publishes estimates of how common variants are at national and regional levels.

U.S. Food and Drug Administration (FDA): The FDA has issued Emergency Use Authorization (EUA) status to a number of molecular, antigen and antibody tests which allows for their marketing and use during the declared Public Health Emergency period for COVID-19 infection. The COVID-19 public health emergency (PHE) declared under section 319 of the Public Health Service (PHS) Act expired on May 11, 2023. Existing emergency use authorizations (EUAs) for devices relating to COVID-19 remain in effect under section 564 of the Federal Food, Drug, and Cosmetic Act.

Detailed information for all FDA EUAs related to COVID-19, including authorizations and fact sheets is available at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covid19euas.

Professional Societies/Organizations:

Centers for Disease Control and Prevention (CDC, 2024): The CDC published the following guidance:

Testing Strategies for SARS-CoV-2

- Diagnostic testing is intended to identify current infection in individuals and should be performed on anyone that has signs and symptoms consistent with COVID-19 or is asymptomatic but has recent known or suspected exposure to someone with COVID-19.
- Viral tests, including nucleic acid amplification tests (NAATs, such as PCR tests), antigen tests and other tests (such as breath tests) are used as diagnostic tests to detect current infection with SARS-CoV-2, determine the need for prevention measures like isolation, and inform an individual's medical care.

Examples of diagnostic testing include:

- Testing individuals with signs or symptoms consistent with COVID-19

- Testing individuals who were exposed to someone with a confirmed or suspected case of COVID-19

Screening Testing
- Screening tests are intended to identify individuals with COVID-19 who are asymptomatic or do not have known, suspected, or reported exposure to someone with COVID-19.
- Screening helps to identify unknown cases so that measures can be taken to prevent further transmission.

Examples of screening include testing:
- Employees in a workplace setting
- Students, faculty, and staff in a school setting
- A person before or after travel
- Someone at home who does not have symptoms associated with COVID-19 and no known exposures to someone with COVID-19

Public Health Surveillance Testing
- Public health surveillance is the ongoing, systematic collection, analysis, and interpretation of health-related data essential to the planning, implementation, and evaluation of public health practice.
- Public health surveillance testing is intended to monitor community- or population-level outbreaks of disease, or to characterize the incidence and prevalence of disease. Surveillance testing involves testing of de-identified specimens and results are not reported back to the individual.
- Public health surveillance testing may sample a certain percentage of a specific population to monitor for increasing or decreasing prevalence, or to determine the population effect from community interventions such as social distancing. Surveillance testing cannot be used for an individual's healthcare decision-making or individual public health actions, such as isolation.

Infectious Disease Society of America (IDSA, 2023): The IDSA published practice guidelines regarding testing for COVID-19, including the following recommendations:

Molecular Diagnostic Testing:
- A SARS-CoV-2 nucleic acid amplification test (NAAT) is recommended in symptomatic individuals suspected of having COVID-19 (strong recommendation, moderate certainty of evidence).
- For symptomatic individuals suspected of having COVID-19, the recommended anatomic site of specimen collection is from either the nasopharynx (NP), anterior nares (AN), oropharynx (OP), or midturbinate regions (MT); saliva, or mouth gargle (conditional recommendation, low certainty evidence).
- For symptomatic individuals suspected of having COVID-19, AN and MT swab specimens may be collected for SARS-CoV-2 RNA testing by either patients or healthcare providers (conditional recommendation, moderate certainty evidence).
- It is suggested to use either rapid or standard laboratory-based NAATs in symptomatic individuals suspected of having COVID-19 (conditional recommendation, moderate certainty of evidence).
- A single NAAT and not repeating testing routinely is suggested in symptomatic or asymptomatic individuals suspected of having COVID-19 whose initial NAAT result is negative with (conditional recommendation, very low certainty of evidence).
- SARS-CoV-2 RNA testing in asymptomatic individuals who are either known or suspected to have been exposed to COVID-19 is suggested (conditional recommendation, moderate

certainty of evidence). Known exposure was defined as direct contact with a laboratory confirmed case of COVID-19.
- For individuals who have clinical or epidemiologic reasons that might make testing desirable, the IDSA panel suggests using either rapid or laboratory-based NAATs in asymptomatic individuals with known exposure to SARS-CoV-2 infection (conditional recommendation, moderate certainty of evidence).
- Routine SARS-CoV-2 NAAT is not recommended in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized (conditional recommendation, very low certainty of evidence). Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19. A low prevalence of COVID-19 in the community was considered communities with a prevalence of <2%.
- The IDSA panel suggests against routine SARS-CoV-2 NAAT of asymptomatic individuals without a known exposure to COVID-19 who are undergoing a medical or surgical procedure (conditional recommendation, very low certainty evidence).
- The IDSA panel suggests against routinely repeating NAAT before medical or surgical procedures in patients with a recent history of COVID-19 (conditional recommendation, very low certainty evidence).
- The IDSA panel suggests against routinely repeating NAAT in patients with COVID-19 to guide release from isolation (conditional recommendation, very low certainty evidence).
- The IDSA panel suggests neither for nor against home-testing for SARS-CoV-2. (evidence gap).

Antigen Testing:
- For asymptomatic individuals with known exposure to SARS-CoV-2 infection, the IDSA panel suggests using a single standard NAAT (either rapid RT-PCR or laboratory-based NAAT) over a single rapid Ag test (conditional recommendation based on moderate certainty in test accuracy of rapid Ag tests and very low certainty in comparative test accuracy of rapid RT-PCR versus rapid Ag tests).
- For asymptomatic individuals with known exposure to SARS-CoV-2 infection, the IDSA panel suggests a single (i.e., one-time) standard NAAT (either rapid RT-PCR or laboratory-based NAAT) rather than a strategy of two consecutive rapid Ag tests (conditional recommendation).
- In asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests neither for nor against using single (i.e. one-time) rapid Ag testing over no testing (evidence gap to inform the utility of Ag testing compared to no testing).
- In asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests neither for nor against using repeat rapid Ag testing over no testing (evidence gap to inform the utility of a strategy of Ag testing compared to no testing).

Serologic (Antibody) Testing:
- The IDSA panel suggests against using serologic testing to diagnose SARS-CoV-2 infection during the first two weeks (14 days) following symptom onset (strong recommendation, low certainty of evidence).
- When evidence of previous SARS-CoV-2 infection is desired, the IDSA panel suggests testing for SARS-CoV-2 IgG, IgG/IgM or total antibody three to five weeks after symptom onset (conditional recommendation, low certainty of evidence).
- The IDSA panel recommends against using IgM antibodies to detect evidence of past SARS-CoV-2 infection (conditional recommendation, low certainty of evidence).
- The IDSA panel recommends against using IgG antibody to provide evidence of COVID-19 infection in symptomatic patients with a high clinical suspicion and repeatedly negative NAAT testing (strong recommendation, very low certainty of evidence). There is no added benefit to assessing anti-SARS-CoV-2 antibodies over repeat NAAT for the diagnosis of

acute COVID-19. No SARS-CoV-2 serologic test can differentiate between recent or remote infection.
- In pediatric patients with multisystem inflammatory syndrome (MIS-C), 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).
- When evidence of prior SARS-CoV-2 infection is desired, the IDSA panel suggests using serologic assays that target nucleocapsid protein rather than spike protein (conditional recommendation, low certainty of evidence). Sensitivity and specificity of nucleocapsid and spike antibody tests are similar and require the clinician to know and understand the antibody target of the test that is used; interpretation of results as indicative of past infection (anti-nucleocapsid) versus past infection or vaccination (anti-spike).
- In individuals with previous SARS-CoV-2 infection or vaccination, the IDSA panel suggests against routine serologic testing given no demonstrated benefit to improving patient outcomes (conditional recommendation, very low certainty of evidence).

National Institutes of Health ([NIH], 2023): The NIH published updated recommendations regarding testing for SAR-Co-V2. In the update, the COVID-19 Treatment Guidelines Panel (the Panel) defers to the Centers for Disease Control and Prevention (CDC) for recommendations on diagnostic testing for SARS-CoV-2 infection and on the use of testing for screening purposes.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD		No National Coverage Determinations found	
LCD	NGS	Respiratory Pathogen Panel Testing/L39027	12/1/2021
LCD	First Coast	Respiratory Pathogen Panel Testing/L38918	7/11/2021
LCD	Novitas	Respiratory Pathogen Panel Testing/L38916	7/11/2021

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:
1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Molecular (Nucleic Acid), Antigen Testing

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
87426	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or

CPT®* Codes	Description
	semiquantitative; severe acute respiratory syndrome coronavirus (eg, SARS-CoV, SARS-CoV-2 [COVID-19])
87428	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; severe acute respiratory syndrome coronavirus (eg, SARS-CoV, SARS-CoV-2 [COVID-19]) and influenza virus types A and B
87635	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), amplified probe technique
87811†	Infectious agent antigen detection by immunoassay with direct optical (ie, visual) observation; severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) (Coronavirus disease [COVID-19])

†Note: Not Covered or Reimbursable when used to report an Over-the-Counter (OTC) test for SARS-CoV-2 (COVID-19) infection.

HCPCS Codes	Description
U0001	CDC 2019 Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel
U0002	2019-nCoV Coronavirus, SARS-CoV-2/2019-nCoV (COVID-19), any technique, multiple types or subtypes (includes all targets), non-CDC

Not Covered or Reimbursable when submitted with one of the CPT® or HCPCS Codes above:

ICD-10-CM Diagnosis Codes	Description
Z11.52	Encounter for screening for COVID-19
Z11.59	Encounter for screening for other viral diseases

Not Covered or Reimbursable when submitted with one of the CPT® or HCPCS Codes and one of the ICD-10 Diagnosis Codes above:

ICD-10-CM Diagnosis Codes	Description
Z20.822	Contact with and (suspected) exposure to COVID-19
Z20.828	Contact with and (suspected) exposure to other viral communicable diseases

Considered Medically Necessary:

ICD-10-CM Diagnosis Codes	Description
	All other codes

Antibody (Serology) Testing

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
86328	Immunoassay for infectious agent antibody(ies), qualitative or semiquantitative, single step method (eg, reagent strip); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19])
86408	Neutralizing antibody, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]); screen
86409	Neutralizing antibody, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]); titer
86413	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) antibody, quantitative
86769	Antibody; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19])
0224U	Antibody, severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) (Coronavirus disease [COVID-19]), includes titer(s), when performed

ICD-10-CM Diagnosis Codes	Description
M35.81	Multisystem inflammatory syndrome
U09.9	Post COVID-19 condition, unspecified

Not Covered or Reimbursable:

ICD-10-CM Diagnosis Codes	Description
	All other codes

<u>Not Covered or Reimbursable</u>

CPT®* Codes	Description
87913	Infectious agent genotype analysis by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]), mutation identification in targeted region(s)
0226U	Surrogate viral neutralization test (sVNT), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), ELISA, plasma, serum

Not Covered or Reimbursable Under Standard Benefit Plan Language:

ICD-10-CM Diagnosis Codes	Description
Z02.0	Encounter for examination for admission to educational institution
Z02.1	Encounter for pre-employment examination
Z02.3	Encounter for examination for recruitment to armed forces
Z02.5	Encounter for examination for participation in sport
Z02.6	Encounter for examination for insurance purposes
Z02.71	Encounter for disability determination
Z02.79	Encounter for issue of other medical certificate
Z02.89	Encounter for other administrative examinations
Z02.9	Encounter for administrative examinations, unspecified

Not Covered or Reimbursable when used to report Tests and Devices for SARS-CoV-2 (COVID-19) infection (e.g., Tiger Tech COVID Plus™) that are Not Diagnostic:

CPT®* Codes	Description
99199	Unlisted special service, procedure or report
E1399	Durable medical equipment, miscellaneous

***Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.**

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Revision Details

Type of Revision	Summary of Changes	Date
Annual review	• No policy statement changes.	6/15/2024