Medical Coverage Policy

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COVID-19: In Vitro Diagnostic Testing

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Overview

This Coverage Policy addresses in vitro diagnostic testing methods to detect the presence of, or suspected exposure to the SARS-CoV-2 virus which causes COVID-19 infection. Molecular tests and antigen tests are considered diagnostic of an active infection with the SARS-CoV-2 virus. In general, antibody (serology) tests are not diagnostic; rather, they are used to identify individuals who have developed antibodies against the SARS-CoV-2 virus and may be used for public health purposes such as population prevalence estimates. The Coverage Policy applies to both individual and pooled testing methods.

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

Coverage Policy

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

Diagnostic and Covered

A molecular or antigen in vitro diagnostic test for SARS-CoV-2 (COVID-19) infection is considered diagnostic and is a covered service with no customer cost share during the declared Public Health Emergency (PHE) period if ALL of the following criteria are met:

- an individual seeks and receives a COVID-19 diagnostic test from a licensed or authorized health care provider **OR**,
- a licensed or authorized health care provider refers an individual for a COVID-19 diagnostic test
- FDA approved or cleared or Emergency Use Authorization (EUA)
- performed by a CLIA-accredited high or medium-complexity or CLIA-waived laboratory (per test Instructions for Use)

An antibody (serology) test for SARS-CoV-2 antibodies is considered diagnostic and is a covered service with no customer cost share during the declared Public Health Emergency (PHE) period when ALL of the following criteria are met:

- an individual seeks and receives a COVID-19 diagnostic test from a licensed or authorized health care provider, **OR**
- a licensed or authorized health care provider refers an individual for a COVID-19 diagnostic test
- FDA approved or cleared or Emergency Use Authorization (EUA)
- performed by a CLIA-accredited high or medium-complexity laboratory (per 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]).

Not Diagnostic and Not Covered

In vitro testing (i.e., molecular, antigen, antibody) is considered not diagnostic and not covered when performed for screening purposes in the general population, including but not limited to the following indications:

- population or public health screening
- determine prevalence of COVID-19 infection in the community
- screening assessment in a congregate setting

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

If the above criteria are not met, in vitro testing (i.e., molecular, antigen, antibody) is not covered, 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.)

- 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 ICD-10 code descriptions.**

Over-the-Counter (OTC) tests for SARS-CoV-2 (COVID-19) infection when the criteria above are not met are not covered.

Tests for SARS-CoV-2 (COVD-19) infection that are not diagnostic and/or do not otherwise meet the criteria above (e.g., Tiger Tech COVID Plus™) are not covered.

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. Common symptoms of COVID-19 infection are fever, chills, cough and shortness of breath, persistent pain or pressure in chest, confusion, inability to wake or stay awake, cyanosis of the lips or face, fatigue, body aches or muscle pain, sore throat, new loss of taste or smell, diarrhea and nausea (Centers for Disease Control and Prevention [CDC], 2021; Infectious Disease Society of America [IDSA], 2020). These symptoms typically appear 2–14 days after exposure. Symptoms can progress rapidly to severe respiratory distress requiring hospitalization, culminating in death.

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, 2020). According to IDSA (2020), seroprevalence data will be important in understanding the scale of the pandemic and future vaccine utility.

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, 2020).

At this time there is no national reference standard for the prevalence rate of COVID-19; rather, it is based on complex mathematical modeling (CDC, 2020). The Infectious Disease Society of America ([IDSA], 2020) notes that low prevalence of COVID-19 corresponds to <2% prevalence of SARS-CoV-2 antibodies within a community. High prevalence corresponds a prevalence of ≥10%. The CDC (2020) 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.

Testing

To control the spread of this disease, it is imperative to test for and diagnose those who have been infected with COVID-19. In vitro diagnostic devices are tests performed on samples taken from the human body, such as swabs of mucus from inside the nose or back of the throat, or blood taken from a vein or finger stick (US Food and Drug Administration [FDA], 2020).

Generally, viral testing for SARS-CoV-2 is considered to be diagnostic when conducted among individuals with symptoms consistent with COVID-19 or among asymptomatic individuals with known or suspected recent exposure to SARS-CoV-2 to control transmission, or to determine resolution of infection. Viral testing is screening when conducted among asymptomatic individuals without known or suspected exposure to SARS-

CoV-2 for early identification, and surveillance when conducted among asymptomatic individuals to detect transmission hot spots or characterize disease trends (CDC, 2020).

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, 2021).

Multiple methods are used in formation and processing of molecular, antigen and antibody tests, including the use of different probes and reagents and interpretation and reporting standards. The FDA has established minimum validation standards for these tests, which are authorized under the Emergency Use Authorization (EUA) designation.

Two types of tests are used for the diagnosis of COVID-19 infection: molecular 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, 2021, 2020; FDA, 2021).

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 (2021, CDC (2021, 2020) and published professional society recommendations (e.g., IDSA, 2021).

According to the CDC (2021), diagnostic testing is intended to identify current infection and is performed when an individual has symptoms consistent with COVID-19, or is asymptomatic but has a recent known or suspected exposure to SARS-CoV-2. Diagnostic testing is indicated for:

- individual with symptoms consistent with COVID-19 who presents to their healthcare provider
- individual who is identified as a result of contact tracing efforts
- individual who indicates that they were exposed to someone with a confirmed or suspected case of COVID-19
- individual who attended an event where another attendee was later confirmed to have COVID-19

Interim Guidance from the CDC (2021) also notes that screening tests are intended to identify infected people who are asymptomatic and do not have known, suspected, or reported exposure to SARS-CoV-2. According to the CDC, screening helps to identify unknown cases so that measures can be taken to prevent further transmission. Screening testing are used for the following:

- employees in a workplace setting
- students, faculty, and staff in a school setting
- travel
- at home by someone who does not have symptoms associated with COVID-19 and no known exposures to someone with COVID-19
- public health surveillance testing (i.e., 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 monitors for increasing or decreasing

prevalence and to determine the population effect from community interventions such as social distancing. Surveillance testing results are not linked to individual people; and therefore, cannot be used for individual decision-making (CDC, 2021).

The CDC notes that not everyone needs to be tested. Recommendations regarding testing for the SARS-CoV-2 virus using diagnostic (molecular or antigen) tests have been published by the CDC (2021):

- Molecular or antigen tests are recommended to diagnose acute infection.
- Testing for SARS-CoV-2 should be conducted in consultation with a healthcare provider
- If an individual does not have COVID-19 symptoms and has not been in close contact with someone known to have SARS-CoV-2 infection (meaning being within 6 feet of an infected person for at least 15 minutes) a test is not needed unless recommended or required by your healthcare provider or public health official.
- If an individual is symptomatic the healthcare provider may advise a SARS-CoV-2 test be performed
- If a test is positive, it does not need to be repeated for at least 3 months.
- Testing should be performed for an individual who has had close contact (within 6 feet for a total of 15 minutes or more) with someone with confirmed COVID-19.
- Testing should be performed for an individual who has taken part in activities that put them at higher risk for COVID-19 because they cannot socially distance as needed, such as travel, attending large social or mass gatherings, or being in crowded indoor settings.
- An individual who has been asked or referred for testing by their healthcare provider, local or state health department should receive a test.
- A healthcare provider in close contact of a person with documented SARS-CoV-2 infection while using recommended personal protective equipment, does not need to be tested.
- Testing is recommended if an individual is in a high SARS-CoV-2 transmission zone and has attended a public or private gathering of more than 10 people (without universal mask wearing and/or physical distancing).
- If an individual works in a nursing home testing is recommended for the following:
    - as part of a nursing home's plan to open or reopen, if the individual has not been previously tested.
    - If there is an outbreak in the facility repeat testing should be performed at regular intervals if the initial test result was negative, until the outbreak is over.
    - Serial testing may be recommended based on county percent test positivity rate.
- If an individual lives in or receives care in a nursing home testing is recommended for the following:
    - as part of a nursing home's plan to open or reopen, if the individual has not been previously tested
    - if there is an outbreak in the facility repeat testing of an individual should be performed at regular intervals if the initial test result was negative, until the outbreak is over
    - If the individual is symptomatic
    - If an individual leaves the facility on a regular basis (e.g. for dialysis or frequent medical/other appointments)
- Testing is recommended for a critical infrastructure worker, healthcare worker, or first responder, according to employer's guidelines.
- A follow-up negative test to return to work or school is not required, as long as the individual did not require hospitalization and it has been at least at least 10 days after symptom onset and resolution of fever for at least 24 hours, without the use of fever-reducing medications, and with improvement of other symptoms.

Regarding public health testing the CDC notes:

- For public health reasons, public health official(s) or healthcare provider(s) may advise specific people, or groups of people, to be tested.

- Your healthcare provider or public health official may recommend that you are tested before being admitted to the hospital or before a procedure (e.g., pregnant people admitted for labor and delivery, surgery).
- In areas where there are a small number of new cases and limited spread, your public health department may request a small number of asymptomatic “healthy people” to be tested.
- If there is significant spread of the virus in your community, your public health department may request significant numbers of asymptomatic “healthy people” to be tested in order to help stop the spread of the virus.
- Approaches for early identification of infected individuals include, initial testing of everyone in the setting, periodic (e.g., weekly) testing of everyone in the setting, and testing of new or returning entrants into the setting.

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. According to the CDC (2020), the “gold standard” for clinical diagnostic detection of SARS-CoV-2 remains nucleic acid amplification tests (NAATs), such as reverse transcription-polymerase chain reaction (RT-PCR) tests. 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. It can identify and quantify the presence of infectious agents in a sample through the process of detection, amplification, and output measurement. Performance has been validated for use in symptomatic individuals; however, is unknown in asymptomatic patients (FDA, 2020).

The FDA further 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 (2020).

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). Molecular tests have high analytical specificity and sensitivity to detect the presence of the virus. 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%.

Testing in asymptomatic individuals or in real-world community samples has not been clinically validated. Results may not be as robust as accuracy will be 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.

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 CDC also recommends that except for rare situations, a test-based strategy is no longer recommended to determine when an individual with SARS-CoV-2 infection is no longer infectious (e.g., to

discontinue transmission-based precautions or home isolation). Evidence supports a symptom-based strategy (CDC, 2021).

The ISDA (2020) published guidelines regarding 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, even when the clinical suspicion for COVID-19 is low.
- 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.
- SARS-CoV-2 RNA testing is recommended in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a low prevalence of COVID-19 in the community. Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19. A low prevalence of COVID-19 in the community is defined by the IDSA as a prevalence of <2%.
- SARS-CoV-2 RNA testing is recommended in asymptomatic individuals with no known contact with COVID-19, who are being hospitalized in areas with a high prevalence of COVID-19 in the community (i.e., hotspots). High prevalence of COVID-19 is defined by the IDSA as a prevalence of ≥10%.

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, 2020). 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, 2020). 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 (FDA, 2020).

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 detects fragments of proteins found on or within the SARS-CoV-2 virus (e.g., nucleocapsid protein 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 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 and a test specificity of 100% is reported. Negative results do not rule out COVID-19.

The FDA (2020) also notes that 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, for patient management (FDA, 2020). 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. The CDC (2020) notes evaluating the results of an antigen test for SARS-CoV-2 should take into account the performance characteristics (e.g., sensitivity, specificity) and the instructions for use of the FDA-authorized assay, the prevalence of SARS-CoV-2 infection in that particular community (positivity rate over the previous 7–10 days or the rate of cases in the community), and the clinical and epidemiological context of the person who has been tested.

An advantage of antigen testing is that the methodology lends itself to adaptation in 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 (Chau et al., 2020). Clinical correlation with patient history and other diagnostic information is necessary to determine infection status.

Regarding antigen tests, the CDC (2020) notes the following:

- Antigen tests that have received EUAs from FDA are authorized for diagnostic testing in symptomatic persons.
- When testing a person who has symptoms associated with COVID-19, indicating that pretest probability is high, the healthcare provider generally can interpret a positive antigen test to indicate that the person is infected with SARS-CoV-2.
- 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.

Antibody (Serology) Testing

Antibody tests detect the body's immune response to the infection caused by the virus rather than detecting the virus itself. Serologic tests detect resolving or past SARS-CoV-2 virus infection indirectly by measuring the person's humoral immune response to the virus (CDC, 2020). 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. Clinical utility for diagnosis has not been established; the relationship between the presence of antibodies and re-infection and or re-activation of the virus is unknown. It is also unclear to what degree the immunologic response persists and continues to be a relevant indicator of the body's immunity. 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.

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 (CDC, 2020; 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, 2020). 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.

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 (FDA, 2020). 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)

Efforts are underway to conduct large-scale validation studies on the performance of these assays, which is 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).

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, 2020). As a result, the clinical utility of serology testing is uncertain.

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, 2020). 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.

Serologic testing by itself should not be used to establish the presence or absence of SARS-CoV-2 infection or reinfection. Antibodies may not be present among those tested early in illness before antibodies develop 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. 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.

Such testing is not recommended as a tool to establish or diagnose SARS-CoV-2 infection (FDA, 2020; CDC, 2020; National Institutes of Health [NIH], 2020). 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, 2020; CDC, 2020). The FDA has not authorized using antibody tests to diagnose SARS-CoV-2 infection, and CDC does not currently recommend using antibody testing as the sole basis for diagnosis of acute infection. 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 (CDC, 2020).

The results of ongoing research are needed before it is known whether antibodies are associated with protection from future infection. Results can help inform who may qualify to donate blood that can be used to manufacture convalescent plasma, an investigational product for use with those who are seriously ill from COVID-19. 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 (2020) notes:

- In general, a positive antibody test is presumed to mean a person has been infected with SARS-CoV-2, the virus that causes COVID-19, at some point in the past. It does not mean they are currently infected.
- Antibody (serology) testing should not be used to establish the presence or absence of SARS-CoV-2 infection or reinfection.
- Antibody test results should not be used to diagnose someone with an active infection or reinfection. Antibodies may not be present among those tested early in illness before antibodies develop 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.
- Antibody tests are not recommended as the sole basis for diagnosis of acute infection.
- In certain situations, serologic assays may be used to support clinical assessment of persons who present late in their illnesses when used in conjunction with viral detection tests. In addition, if a person is suspected to have a post-infectious syndrome caused by SARS-CoV-2 infection (e.g., Multisystem Inflammatory Syndrome in Children; MIS-C), serologic assays may be used.
- Currently, there is no identified advantage whether the assays test for IgG, IgM and IgG, or total antibody.
- Serologic tests have several important applications in monitoring and responding to the COVID-19 pandemic.
- From a public health perspective, serologic assays for SARS-CoV-2 can have a role in understanding the transmission dynamic of the virus in the general population and identifying groups at higher risk for infection.
- Antibody tests should not be used to determine a person's immune status until evidence confirms that antibodies provide protection; how much antibody is protective; and how long protection lasts.

Multisymptom Inflammatory Syndrome in Children (MIS-C)

Most children are asymptomatic or exhibit mild symptoms from COVID-19 infection; however, a small number of children develop a significant systemic inflammatory response. This rare syndrome shares common features with other inflammatory conditions such as Kawasaki disease, staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis and macrophage activation syndromes. It can also present with unusual abdominal symptoms with excessive inflammatory markers (Royal College of Paediatrics and Child Health [RCPCH], 2020). An individual with MIS-C is defined by the CDC (2020) as ≤21 years presenting with fever (i.e. fever >38.0C for ≥24 hours, or report of subjective fever ≥24 hours). There is laboratory evidence of inflammation (e.g., an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin) and evidence of clinically severe illness requiring hospitalization. Other symptoms include involvement of >2 organs (e.g., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) and no alternative plausible diagnoses; and positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test and/or COVID-19 exposure within the 4 weeks prior to the onset of symptoms (CDC, 2021).

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.

Multisymptom Inflammatory Syndrome in Adults (MIS-A)
Adults who have been infected with the SARS-CoV-2 virus can develop symptoms of MIS-A days to weeks after getting sick. Symptoms are varied and may include fever, low blood pressure, abdominal (gut) pain, vomiting, diarrhea, neck pain, rash, chest tightness/pain and fatigue. MIS-A occurs less often than MIS-C and little is known. Researchers continue to gather data to identify who is at risk and how it affects adults. Further research is needed to understand the pathogenesis and long-term effects of this condition (CDC, 2020).

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. Screening includes broad screening of individuals prior to development of symptoms 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, 2020).

Surveillance for COVID-19 is not regulated by the FDA, rather is generally a testing plan developed by a State Public Health Department. 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, 2020).

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 and are considered Not Diagnostic and Not Covered. One example is the Tiger Tech COVID Plus™ monitor ([Tiger Tech Solution, Inc., Miami, FL]). According to the package insert, this monitor involves the use of an armband with two embedded photoplethysmography (PPG) sensors and a processor. The sensors acquire direct pulsatile biosignals over a period of 3-5 minutes. The processor interprets the signals via a probabilistic

machine learning model that has been trained to make predictions on whether the individual is showing morphological features that have been correlated with certain conditions, including a hypercoagulable state. The package insert notes that the monitor is not a diagnostic device, and must not be used to diagnose or exclude SARS-CoV-2 infection.

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U.S. Food and Drug Administration (FDA)

At present there are no FDA approved tests to detect the SARS-CoV-2 virus or to determine the presence of antibodies to the virus. 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.

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

American Academy of Family Physicians ([AAFP], 2020): The AAFP notes that family physicians should use their best clinical judgement to determine who should be tested.

Centers for Disease Control and Prevention (CDC, 2021, 2020): The CDC published an overview of testing for healthcare professionals, including the following:

- Authorized assays for viral testing include those that detect SARS-CoV-2 nucleic acid or antigen.
- CDC does not currently recommend using antibody testing as the sole basis for diagnosis of acute infection, and antibody tests are not authorized by FDA for such diagnostic purposes. In certain situations, serologic assays may be used to support clinical assessment of persons who present late in their illnesses when used in conjunction with viral detection tests. In addition, if a person is suspected to have post-infectious syndrome (e.g., Multisystem Inflammatory Syndrome in Children) caused by SARS-CoV-2 infection, serologic assays may be used.
- Recommends the use of authorized nucleic acid or antigen detection assays that have received an FDA EUA to test persons with symptoms when there is a concern of potential COVID-19. Tests should be used in accordance with the authorized labeling; providers should be familiar with the tests' performance characteristics and limitations.
- Describes strategies to determine when a person with SARS-CoV-2 infection no longer requires isolation or work exclusion and for public health surveillance
- Notes serologic assays can play role in understanding transmission of the virus in the general population and identify groups of higher risk of infection. Antibody tests help determine whether the individual being tested was previously infected—even if that person never showed symptoms.

Infectious Disease Society of America (IDSA, 2020): The IDSA published practice guidelines regarding testing for COVID-19, including the following recommendations:

- A SARS-CoV-2 nucleic acid amplification test (NAAT) is recommended in symptomatic individuals in the community suspected of having COVID-19, even when the clinical suspicion for COVID-19 is low (strong recommendation, very low certainty of evidence).
- A single viral RNA test and not repeating testing is suggested in symptomatic individuals with a low clinical suspicion of COVID-19 (conditional recommendation, low certainty of evidence).
- Repeating viral RNA testing when the initial test is negative (versus performing a single test) is suggested in symptomatic individuals with an intermediate or high clinical suspicion of COVID-19 (conditional recommendation, low certainty of evidence). Intermediate/high clinical suspicion typically applies to the hospital setting and is based on the severity, numbers and timing of compatible clinical signs/symptoms.
- Using either rapid RT-PCR or standard laboratory based NAAT over rapid isothermal NAATs in symptomatic individuals suspected of having COVID-19 is suggested (conditional recommendation, 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, very low certainty of evidence). Known exposure was defined as direct contact with a laboratory confirmed case of COVID-19.
- SARS-CoV-2 RNA testing in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a low prevalence of COVID-19 in the community is suggested (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%.
- Direct SARS-CoV-2 RNA testing in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a high prevalence of COVID-19 in the community (i.e., hotspots) is recommended (conditional recommendation, very low certainty of evidence). Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19. A high prevalence of COVID-19 in the community was considered communities with a prevalence of ≥10%.
- SARS-CoV-2 RNA testing in immunocompromised asymptomatic individuals who are being admitted to the hospital regardless of exposure to COVID-19 is recommended (strong recommendation, very low certainty of evidence). Immunosuppressive procedures are defined as cytotoxic chemotherapy, solid organ or stem cell transplantation, long acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids.
- SARS-CoV-2 RNA testing (versus no testing) in asymptomatic individuals before immunosuppressive procedures regardless of a known exposure to COVID-19 is recommended (strong recommendation, very low certainty of evidence). Immunosuppressive procedures are defined as cytotoxic chemotherapy, solid organ or stem cell transplantation, long acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids.
- The IDSA panel makes no recommendations for or against SARS-CoV-2 RNA testing before initiating immunosuppressive therapy in asymptomatic individuals with cancer (evidence gap).
- The IDSA panel makes no recommendations for or against SARS-CoV-2 RNA testing before the initiation of immunosuppressive therapy in asymptomatic individuals with autoimmune disease (evidence gap).
- SARS-COV-2 RNA testing in asymptomatic individuals (without known exposure to COVID-19) who are undergoing major time-sensitive surgeries is suggested (conditional recommendation, very low certainty of evidence). Time-sensitive surgery is defined as medically necessary surgeries that need to be done within three months. Testing should ideally be performed as close to the planned surgery as possible (e.g. within 48-72 hours).
- SARS-CoV-2 RNA testing in asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when PPE is available is not suggested (conditional recommendation, very low certainty of evidence). Time-sensitive procedures defined as medically necessary procedures that need to be done within three months. Procedures considered to be aerosol generating (i.e., bronchoscopy, open suctioning of airways, sputum induction, cardiopulmonary resuscitation, endotracheal intubation and extubation, non-invasive ventilation (e.g., BiPAP, CPAP), bronchoscopy, manual ventilation)
- SARS-CoV-2 RNA testing in asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when PPE is limited, and testing is available is suggested (conditional recommendation, very low certainty of evidence). Time-sensitive procedures are defined as medically necessary procedures that need to be done within three months. Testing should be performed as close to the planned procedure as possible (e.g. within 48-72 hours). Decisions about PPE will be dependent on test results because of limited availability of PPE. However, there is a risk for false negative test results, so caution should be exercised for those who will be in close contact with/exposed to the patient's airways. Procedures considered to be aerosol generating (i.e., bronchoscopy, open suctioning of airways, sputum induction, cardiopulmonary resuscitation, endotracheal intubation and extubation, non-invasive ventilation (e.g., BiPAP, CPAP), bronchoscopy, manual ventilation). The decision to test asymptomatic patients will be dependent on the

availability of testing resources. This recommendation does not address the need for repeat testing if patients are required to undergo.

The IDSA also notes potential utility of antibody (serology) testing in SARS-CoV-2 includes:

- detection of PCR-negative cases, especially for patients who present late with a very low viral load below the detection limit of RT-PCR assays, or when lower respiratory tract sampling is not possible;
- identification of convalescent plasma donors;
- epidemiologic studies of disease prevalence in the community;
- verification of vaccine response once antibody correlate(s) of protection identified

National Institutes of Health ([NIH], 2021): The NIH published the following guidance regarding virologic and serologic testing for SARS-CoV-2 infection:

- In asymptomatic persons, a NAAT should not be repeated within 90 days of previous SARS-CoV-2 infection, even following a significant exposure to SARS-CoV-2 (AIII).
- Because of reports of SARS-CoV-2 reinfection after an initial diagnosis of infection, a NAAT should be considered for persons who have recovered from previous infection and present with symptoms compatible with SARS-CoV-2 infection, in the absence of an alternative diagnosis (BIII).
- Recommends against the use of serologic testing as the sole basis for diagnosis of acute SARS-CoV-2 infection (AIII).
- Recommends against the use of serologic testing to determine whether a person is immune to SARS-CoV-2 infection (AIII).
- . Recommends serologic tests should not be used to:
  - Make decisions about the grouping of persons residing in or being admitted to congregate settings (e.g., schools, dormitories, correctional facilities), or
  - Determine whether persons should return to the workplace.
  - Assess for prior infection solely to determine whether to vaccinate an individual
  - Assess for immunity to SARS-CoV-2 following vaccination, except in clinical trials

Rating of Recommendations: A = Strong, Rating of Evidence: III = Expert opinion

Use Outside of the US
No relevant information

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	N/A	
LCD	Noridian Healthcare Solutions, LLC	MolDX: Multiplex Nucleic Acid Amplified Tests for Respiratory Viral Panels (L37301)	10/01/2019
LCD	CGS Administrators, LLC	MolDX: Multiplex Nucleic Acid Amplified Tests for Respiratory Viral Panels (L37348)	1128/2019
LCD	Palmetto GBA	MolDX: Multiplex Nucleic Acid Amplified Tests for Respiratory Viral Panels (L37713)	11/02/2019
LCD	Wisconsin Physicians Service Insurance Corporation	MolDX: Multiplex Nucleic Acid Amplified Tests for Respiratory Viral Panels (L37764)	11/28/2019

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Diagnostic and Covered

Molecular (Nucleic Acid), Antigen Testing

CPT®* Codes	Description
87426	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; 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
87636	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) (Coronavirus disease [COVID-19]) and influenza virus types A and B, multiplex amplified probe technique
87637	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) (Coronavirus disease [COVID-19]), influenza virus types A and B, and respiratory syncytial virus, multiplex 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])
0240U	Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 3 targets (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], influenza A, influenza B), upper respiratory specimen, each pathogen reported as detected or not detected
0241U	Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 4 targets (severe acute respiratory syndrome coronavirus [SARS-CoV-2], influenza A, influenza B, respiratory syncytial virus [RSV]), upper respiratory specimen, each pathogen reported as detected or not detected

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
U0003	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) amplified probe technique, making use of high throughput technologies as described by CMS-2020-01-R
U0004	2019-nCoV Coronavirus, SARS-CoV-2/2019-nCoV (COVID-19), any technique, multiple types or subtypes (includes all targets), non-CDC, making use of high throughput technologies as described by CMS-2020-01-R

HCPCS Codes	Description
U0005	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, CDC or non-CDC, making use of high throughput technologies, completed within 2 calendar days from date and time of specimen collection. (List separately in addition to either HCPCS code U0003 or U0004)

Antibody (Serology) Testing

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
	All other codes not listed in the Not Medically Necessary section directly below

Considered Not Medically Necessary when submitted with one of the CPT® codes above:

ICD-10-CM Diagnosis Codes	Description
Z01.84	Encounter for antibody response examination

Considered Not Medically Necessary:

CPT®* Codes	Description
0226U	Surrogate viral neutralization test (sVNT), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), ELISA, plasma, serum

Not Covered

Considered Not Covered 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 when used to report Non Diagnostic Tests and Devices for SARS-CoV-2 (COVD-19) infection (e.g., Tiger Tech COVID Plus™).

CPT®* Codes	Description
99199	Unlisted special service, procedure or report

HCPCS Codes	Description
E1399	Durable medical equipment, miscellaneous

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