

# 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 and have discretion in making individual coverage determinations. 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 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, serology (antibody) 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 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 as directed by Federal Mandate if ALL of the following criteria are met:**

- ANY of the FOLLOWING:
  - an individual seeks and receives a COVID-19 diagnostic test from a licensed or authorized health care provider (HCP) **OR**,
  - a licensed or authorized health care provider refers an individual for a COVID-19 diagnostic test **OR**,
  - over the counter at-home rapid antigen COVID-19 diagnostic tests (limited to eight (8) tests per month per covered individual) when purchased from established retailers that would typically be expected to sell OTC COVID-19 tests.
- test is FDA approved or cleared or has an Emergency Use Authorization (EUA)
- performed by a CLIA-accredited 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 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:**

- 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
- population or public health screening
- 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.)**

- 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 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 (COVID-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. 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, 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], 2022; Infectious Disease Society of America [IDSA], 2021). 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, 2022). 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).

### Racial and Ethnic Health Disparities

According to the CDC, some racial and ethnic minority groups are disproportionately affected by COVID-19 (2022). The CDC recognizes five 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:

- neighborhood and physical environment
- health and healthcare
- occupation and job conditions
- income and wealth and education

A COVID-19 Response Health Equity Strategy to outline a plan to reduce the disproportion burden of COVID-19 among racial and minority populations has been developed by the CDC. To that end, the reporting of race and ethnicity data is required of labs and testing facilities by the U.S. Department of Health and Human Services.

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 national data tracked by the CDC (2021), people in racial and ethnic minority groups are more likely to live in areas with high rates of new COVID-19 infections and have higher rates of death caused by COVID-19:

Race/Ethnicity	Percent of cases	Percent of US population
Hispanic/Latino	27.4	18.45
American Indian / Alaska Native, Non-Hispanic	1.1	0.74
Asian, Non-Hispanic	3.1	5.76
Black, Non-Hispanic	11.8	12.54
Native Hawaiian / Other Pacific Islander, Non-Hispanic	0.3	0.182
White, Non-Hispanic	51	60.11
Multiple/Other, Non-Hispanic	5.3	2.22

Likewise, the percent of deaths attributed to COVID-19 infection is dependent on ethnicity. The CDC notes a disproportionate number of deaths attributed to individuals of color:

Race/Ethnicity	Percent of deaths	Percent of US population
Hispanic/Latino	18.2	18.45
American Indian / Alaska Native, Non-Hispanic	1.2	0.74
Asian, Non-Hispanic	3.7	5.76
Black, Non-Hispanic	13.8	12.54
Native Hawaiian / Other Pacific Islander, Non-Hispanic	0.2	0.182
White, Non-Hispanic	59	60.11
Multiple/Other, Non-Hispanic	3.8	2.22

Karaye and Horney (2020) found that local population-level factors related to racial and ethnic minority status, language spoken, housing, transportation, household composition and disability were associated with higher rates of new COVID-19 infections. These findings further support potential links between local social factors and COVID-19. Resources must be equitably available for everyone to maintain physical and mental health. Resources include easy access to information, goods and services, affordable testing, and medical and mental healthcare that are all tailored to meet the needs of people from diverse communities.

Social determinants of health may also influence access to testing. Delays in testing may result in a delay seeking care when sick as well as delays in self-isolation or implementing other mitigation measures that could reduce the spread of the virus to others (CDC, 2021).

A study by Rader et al. (2020) reported that the median travel time to a COVID-19 testing site was 20 minutes in April 2020. Counties with a travel time of more than 20 minutes to a COVID-19 testing site had a higher

percentage of the population that were from racial and ethnic minority groups, were uninsured, and had lower population density (were rural). Data suggest differences in travel time may limit access to, and use of, testing services for those who have limited access to transportation and who live in areas with fewer public transit services and schedules. The authors note other factors that may affect both access to, and use of, testing services include lack of health insurance, concern about the costs or co-pays, occupational factors (e.g., not being able to take time off of work, lack of paid leave, lack of accessible options for people with disabilities, and distrust of the government and healthcare systems). Delays in testing may also delay seeking care when sick as well as delays in self-isolation or implementing other mitigation measures that could reduce the spread of the virus to others (CDC, 2021).

## 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, (2022), CDC (2022, 2021) and published professional society recommendations (e.g., IDSA, 2021).

To control the spread of COVID-19, it is imperative to test for and diagnose those who have been infected with COVID-19. 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: molecular nucleic acid amplification tests 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, 2022; FDA, 2022).

Regarding a testing strategy for COVID-19 diagnostic testing and screening, the CDC (2022) notes the following:

- 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.
- Screening tests are intended to identify unvaccinated people with COVID-19 who are asymptomatic and do not have known, suspected, or reported exposure to SARS-CoV-2. 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
- 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 and have received an Emergency Use Authorization from the U.S. Food and Drug Administration (FDA) or be offered under the policies in FDA's Policy for COVID-19 Tests.
- 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 is performed on de-identified specimens, and thus, results are not linked to individual people. Public health surveillance testing results cannot be used for individual decision-making. Tests used for SARS-CoV-2 public health surveillance on de-identified human specimens do not need to meet FDA and CLIA requirements for diagnostic and screening testing (CDC, 2022).

The CDC notes that SARS-CoV-2 testing may be incorporated as part of a comprehensive approach to reducing transmission. Symptom screening, testing, and contact tracing are strategies to identify people infected with SARS-CoV-2 so that actions can be taken to slow and stop the spread of the virus.

Regarding the need for testing, the CDC notes (2022) the following individuals should get tested for COVID-19:

- If symptoms of COVID-19 are present
- contact with someone who has COVID-19
- an individual who is not up-to-date with COVID-19 vaccines and is prioritized for expanded community screening
- an individual referred to get tested by school, workplace, HCP, state, tribal, local or territorial health department

An individual who has tested positive for COVID-19 within the past three months and recovered does not need to be tested, as long as they do not develop new symptoms (2022).

Point-of care serial screening testing can provide rapid results and is critical to identifying people with COVID-19 who do not have symptoms and slowing the spread of SARS-CoV-2. 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, 2022).

### **Diagnostic Tests**

Diagnostic testing includes testing an individual:

- with symptoms consistent with COVID-19, regardless of vaccination status
- as a result of contact tracing efforts
- who indicates they have had close contact exposure with someone suspected or confirmed as having COVID-19 (CDC, 2022)

### **Screening Tests**

Screening tests are recommended for an individual with no symptoms, and no known, suspected or reported close contact exposure to COVI-19. Guidance from the CDC (2022) notes 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

Regarding screening testing as a prevention strategy the CDC notes:

- Screening testing can improve detection of SARS-CoV-2.
- Serial testing (within cohorts) with rapid isolation of infected individuals may facilitate re-opening of businesses, communities, and schools (in-person instruction in K-12 schools<sup>4</sup>) with less risk of a surge in local cases.
- Frequent testing (1–2 times per week) combined with other risk reduction strategies, contributed to low case rates in university settings
- Frequency of testing could be informed by
  - the current level of community transmission in addition to other known factors about the epidemiology of transmission in a particular cohort. If community transmission is substantial or high, more frequent screening might be needed regardless of other indicators.
  - characteristics (e.g., size, proximity of people, duration of interaction) of the school, workplace, residential setting, or gathering.

- Testing using a tiered approach, analogous to testing described in high-density critical workplace and institutes of higher education guidance, could be considered and might be particularly important for low incidence areas. Such as on some school campuses (e.g., institutes of higher learning), unvaccinated students may be tested upon arrival on campus or upon return from extended breaks

The CDC also notes:

- Molecular or antigen tests are recommended to diagnose acute infection.
- Persons with signs or symptoms of COVID-19 should have diagnostic testing.
- Point-of care serial screening can provide rapid results and be critical to identifying asymptomatic cases needed to interrupt SARS-CoV-2 transmission. This is especially important when community risk or transmission levels are substantial or high.
- The selection and interpretation of SARS-CoV-2 tests should be based on the context in which they are being used, including the prevalence of SARS-CoV-2 in the population being tested.
- Vaccination status should not affect the results of viral testing for SARS-CoV-2. Testing for SARS-CoV-2 should be conducted in consultation with a healthcare provider
- A negative antigen test in persons with signs or symptoms of COVID-19 should be confirmed by NAAT, a more sensitive test.
- In instances of higher pretest probability, such as high incidence of infection in the community, or a person with household or continuous contact to a person with COVID-19, clinical judgement should determine if a positive antigen result for an asymptomatic person should be followed by a laboratory-based confirmatory NAAT.
- Identifying close contacts (people who have been within 6 feet for a combined total of 15 minutes or more during a 24-hour period) of persons with COVID-19 can help reduce the spread of SARS-CoV-2 in communities, workplaces, and schools when these close contacts quarantine themselves. Viral testing is recommended for individuals who are close contacts of persons with COVID-19.
- Fully vaccinated people who have a known exposure to someone with suspected or confirmed COVID-19 should get tested 3-5 days after exposure
- People who are not fully vaccinated should be tested immediately after being identified, and, if negative, tested again in 5–7 days after last exposure or immediately if symptoms develop during quarantine. Most people with a history of test-confirmed COVID-19 who remain asymptomatic after recovery do not need to retest or quarantine if another exposure occurs within 90 days of their initial infection.
- Adults with more severe illness or who are immunocompromised may remain infectious up to 20 days or longer after symptom onset, so a test-based strategy could be considered in consultation with infectious disease experts for these people. For all others, a test-based strategy is no longer recommended except to discontinue isolation or precautions earlier than would occur under the symptom-based strategy.
- Serial testing of unvaccinated persons, regardless of signs or symptoms, is a key component to a layered approach to preventing the transmission of SARS-CoV-2. Screening allows early identification and isolation of persons who are asymptomatic, presymptomatic, or have only mild symptoms and who might be unknowingly transmitting virus. Screening testing may be most valuable in areas with substantial or high community transmission levels (Table 2), in areas with low vaccination coverage, and in certain settings
- 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 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

### **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, 2022).

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, 2022) 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.

### **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. 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.

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 (2021).

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%. 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 IDSA (2021) 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.
- A single SARS-CoV2 viral RNA test is suggested in symptomatic individuals with a low clinical suspicion of COVID-19. Repeated testing is not suggested for this population.
- When the initial viral RNA test is negative repeating the test in a symptomatic individual with an intermediate or high clinical suspicion of COVID-19 is suggested.
- 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.
- SARS-CoV-2 RNA testing is recommended in an asymptomatic individual with no known contact with COVID-19 who are being hospitalized in areas with a low prevalence of COVID-19 in the community. An asymptomatic individual is defined as an individual 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%. This recommendation does not apply to an immunocompromised individual or an individual undergoing time-sensitive major surgery or aerosol generating procedures.
- 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%.
- SARS-CoV-2 RNA testing is recommended in an immunocompromised asymptomatic individual who are being admitted to the hospital, regardless of exposure to COVID-19
- SARS-CoV-2 RNA testing (versus no testing) is recommended in an asymptomatic individual before hematopoietic stem cell (HSCT) or solid organ transplantation (SOT) regardless of a known exposure to COVID-19
- 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 (2022). In general, the larger the pool of specimens, the higher the likelihood of generating false negative results (CDC, 2022). 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 and a 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.

The FDA (2020) 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>. 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, 20202).

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 (2022) 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

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, 2022; CDC, 2022; National Institutes of Health [NIH], 2021). 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, 2021).

Serology tests detect the presence of antibodies in the blood from the body's adaptive immune response to an infection, like COVID-19. They do not detect the virus itself. In the early days of an infection when the body's adaptive immune response is still building, antibodies may not be detected. This limits the test's effectiveness for diagnosing current COVID-19 and is one reason serology tests should not be used to diagnose or exclude acute COVID-19 infection. 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, 2022; 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. 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, 2022; 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.

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, 2022). 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 (FDA, 2022). 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).

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.

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.

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 (MIS-C) and in adults (MIS-A) (CDC, 2022).

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:

- A positive antibody test result shows you may have antibodies from a previous infection or from vaccination for the virus that causes COVID-19.
- Antibody (serology) testing does not replace virologic testing and should not be used to establish the presence or absence of SARS-CoV-2 infection or reinfection.
- 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 with a previous negative antibody test (i.e., seroconversion) and who did not receive a positive viral test may 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 illness, such as multisystem inflammatory syndrome and other post-acute sequelae of COVID-19.
- When serologic tests are used to support diagnosis of recent COVID-19 illness, a single positive antibody test result may reflect previous SARS-CoV-2 infection rather than the most recent illness.
- Serologic testing can be used for clinical, occupational health, and public health purposes, such as serologic surveys, to help differentiate natural infection from vaccination by utilizing tests that measure antibodies against different protein targets.
- Serologic tests can be used in seroprevalence studies to estimate the cumulative incidence of infection (or vaccination) in a community.
- Antibody testing is not currently recommended to assess for immunity to COVID-19 following COVID-19 vaccination or to assess the need for vaccination in an unvaccinated person.
- FDA has issued an EUA for a competitive neutralization test (cVNT), a qualitative binding assay that detects antibodies that block the interaction between the virus and the cellular virus receptor (ACE-2). Although the cVNT exhibits correlation to a plaque reduction neutralization test, the clinical or public health applicability has not been established.
- The clinical and public health applicability of semi-quantitative tests has not been established.
- Tests issued EUA by the Food and Drug Administration (FDA) are recommended for clinical and public health purposes.
- Currently, there is no identified advantage whether the assays test for IgG, IgM and IgG, or total antibody.
- 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.

### **Multisystem 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 organs (CDC, 2022). 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. 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). The CDC has developed a case definition for MIS in adults (MIS-A) and updated the case definition for MIS in children (MIS-C):

### **Adults (MIS-A)**

- General Criteria
  - An individual  $\geq 21$  years hospitalized for  $\geq 24$  hours 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 ( $\geq 38.0^{\circ}\text{C}$  for  $\geq 24$  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

- rash and non-purulent conjunctivitis
- Secondary Clinical Criteria
  - new onset neurologic signs and symptoms
  - shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy)
  - abdominal pain
  - 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 during the current illness by RT-PCR, serology or antigen detection

### Children (MIS-C)

- An individual aged <21 years presenting with fever\*, laboratory evidence of inflammation\*\*, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (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; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

\*Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

\*\*Including, but not limited to, one or more of the following: 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

The CDC notes SARS-Co-V2 detection by RT-PCR is indicated. Where feasible, SARS-Co-V2 serologic testing is suggested, even in the presence of positive results from RT-PCR or antigen testing. Serologic testing should be performed prior to administration of intravenous immunoglobulin (IVIG) or any other exogenous antibody treatments.

### 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 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.

#### **U.S. Food and Drug Administration (FDA)**

At present there is no single pathogen test that has received full FDA approval 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, 2022):** 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.
- A laboratory-based Nucleic Acid Amplification Test (NAAT) is recommended for diagnostic testing of vaccinated, asymptomatic individuals following recent known or suspected exposure to SARS-CoV-2.

Examples of diagnostic testing include:

- Testing anyone with symptoms consistent with COVID-19
- Testing vaccinated and unvaccinated people who were exposed to someone with a confirmed or suspected case of COVID-19

#### Screening Testing

- Screening tests are intended to identify unvaccinated people with COVID-19 who are asymptomatic and do not have known, suspected, or reported exposure to SARS-CoV-2.
- 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.
- 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

**Infectious Disease Society of America (IDSA, 2020):** 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 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  $\geq 10\%$ .
- 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.

#### Antigen Testing:

- For asymptomatic individuals with risk for 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 risk for 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 based in moderate certainty in test accuracy of molecular testing and an evidence gap to inform the test accuracy of a strategies using repeat Ag testing).
- 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:

- 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 recommendations regarding testing for SAR-CoV-2:

- To diagnose acute infection of SARS-CoV-2, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using a nucleic acid amplification test (NAAT) with a sample collected from the upper respiratory tract (i.e., a nasopharyngeal, nasal, or oropharyngeal specimen) (AIII).
- For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:
  - The Panel recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative (BII).
  - The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 (BII).
- A NAAT should not be repeated in an asymptomatic person within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2 (AIII).
- SARS-CoV-2 reinfection has been reported in people who have received an initial diagnosis of infection; therefore, a NAAT should be considered for persons who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis (BIII).
- The Panel recommends against the use of serologic (i.e., antibody) testing as the sole basis for diagnosis of acute SARS-CoV-2 infection (AIII).
- The Panel recommends against the use of serologic (i.e., antibody) testing to determine whether a person is immune to SARS-CoV-2 infection (AIII).
- Based on current knowledge, serologic tests should not be used to (AIII):

- Make decisions about how to group persons in congregate settings (e.g., schools, dormitories, correctional facilities)
- Determine whether persons may 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, B = Moderate

Rating of Evidence: IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; 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)	11/30/2020
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)	10/29/2020

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], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or 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

<b>CPT®* Codes</b>	<b>Description</b>
	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

<b>HCPCS Codes</b>	<b>Description</b>
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) (Coronavirus disease [COVID-19]), 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
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 of specimen collection (List separately in addition to either HCPCS code U0003 or U0004) as described by CMS-2020-01-R2

### **Antibody (Serology) Testing**

<b>CPT®* Codes</b>	<b>Description</b>
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

<b>CPT®* Codes</b>	<b>Description</b>
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

<b>ICD-10-CM Diagnosis Codes</b>	<b>Description</b>
	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:**

<b>ICD-10-CM Diagnosis Codes</b>	<b>Description</b>
Z01.84	Encounter for antibody response examination

**Considered Not Medically Necessary:**

<b>CPT®* Codes</b>	<b>Description</b>
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:**

<b>ICD-10-CM Diagnosis Codes</b>	<b>Description</b>
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 (COVID-19) infection (e.g., Tiger Tech COVID Plus™).**

<b>CPT®* Codes</b>	<b>Description</b>
99199	Unlisted special service, procedure or report

HCPCS Codes	Description
E1399	Durable medical equipment, miscellaneous

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