

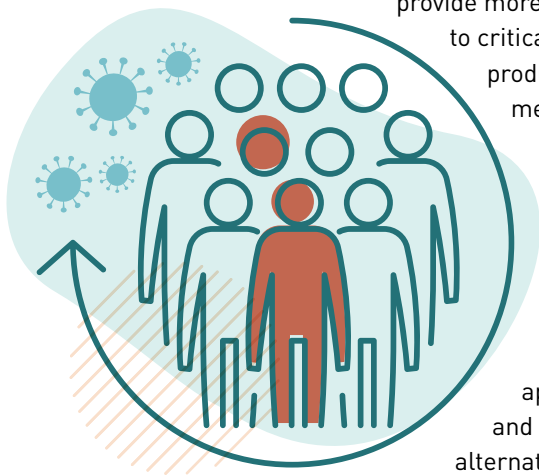
## A Closer Look at Coronavirus Disease 2019 (COVID-19) Diagnostic Testing

The FDA has worked around the clock to help increase the availability of critical medical products, including diagnostic tests, to fight the coronavirus disease 2019 (COVID-19) pandemic.

A patient and consumer [overview](#)<sup>1</sup> of COVID-19 testing has plain language information about both diagnostic and antibody testing for COVID-19. This companion resource takes a closer look at diagnostic testing for COVID-19 and may be of interest to health care providers, test purchasers, and other public health professionals.

### COVID-19 Diagnostic Tests

In certain types of emergencies, the FDA can issue an emergency use authorization, known as an EUA, to provide more timely access to critical medical



products (including medicines and tests) that may help during the emergency when there are no adequate, approved, and available alternative options.

The FDA has authorized for emergency use [tests](#)<sup>2</sup> that can diagnose infection with the virus that causes COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2.

### Emergency Use Authorization

The EUA process is different than FDA approval, clearance, or licensing because the EUA standard requires less evidence than the full approval, clearance, or licensing standard. Under an EUA, the data must show that a product may be effective and that the known and potential benefits outweigh the known and potential risks. This enables the FDA to authorize the emergency

use of medical products that meet the criteria within days or weeks rather than months to years.

The FDA has prioritized review of EUA requests for tests where authorization would increase testing accessibility (such as point-of-care (POC) tests, home collection tests, and at-home tests) or would significantly increase testing capacity (such as tests that reduce reliance on test supplies and high-throughput, widely distributed tests).

### Test performance

No test is 100% accurate, and test performance can vary based on the prevalence of disease in the population being tested. COVID-19 diagnostic tests may be less accurate in populations with a low prevalence of disease and in asymptomatic individuals, individuals who shed little virus, or individuals who are early or late in the course of illness.

Tests are assessed based on their sensitivity and specificity. A test's **sensitivity** is the fraction of positive cases that the test correctly identifies as positive, and a test's **specificity** is the fraction of negative cases that the test correctly identifies as negative.

- A highly sensitive test will generally have a low false negative rate but will run a risk of false positives if the test's specificity is low.
- A highly specific test will generally have a low false positive rate but will run a risk of false negatives if the test's sensitivity is low.

To help mitigate the impact of false results, most

<sup>1</sup> <https://www.fda.gov/consumers/consumer-updates/coronavirus-testing-basics>

<sup>2</sup> <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas>

	MOLECULAR TEST	ANTIGEN TEST
<b>Detects</b>	Viral genetic material, through multiple amplification cycles in PCR testing	Protein(s) from a virus particle
<b>Sample type</b>	Nasal swab, nasopharyngeal swab, mid-turbinate swab, respiratory aspirate/lavage, or saliva sample, depending on the test	Nasal swab or nasopharyngeal swab, depending on the test
<b>Laboratory, point-of-care, or at-home</b>	Most tests are authorized for use in traditional laboratories. A few tests are authorized for use at the point-of-care. Some tests are authorized for at-home sample collection and the patient mails the sample to a traditional laboratory for analysis. Some tests are authorized to be used completely at home with results provided in minutes.	Most tests are authorized for use at the point-of-care.
<b>Turnaround time</b>	Several hours to days for traditional laboratory tests; less than an hour for point-of-care tests; minutes for at-home tests	Less than an hour
<b>Sensitivity and specificity</b>	Generally highly sensitive (especially traditional laboratory PCR tests) and highly specific	Generally highly specific, but less sensitive than molecular tests

COVID-19 tests are prescription-only, so that clinicians order and can then interpret results for patients. Any tests authorized for non-prescription use state in the authorization that they are for “direct-to-consumer” (DTC) or “over-the-counter” (OTC) use, and the patient labeling directs patients to consult their health care provider.

### Molecular versus antigen tests

Currently authorized SARS-CoV-2 diagnostic tests operate using one of two different underlying technological principles. These two diagnostic test types are **molecular tests** and **antigen tests**. Each type of test detects a different part of the SARS-CoV-2 virus particle.

1. **Molecular tests** detect the genetic material or nucleic acid present *inside* a virus particle. The FDA has authorized molecular tests for use in a traditional laboratory setting and authorized some for use in a point-of-care (POC) setting. Most molecular tests are polymerase chain reaction (PCR) tests, also called nucleic acid amplification tests (NAAT). In PCR testing, a machine located in a traditional laboratory or a POC setting, depending on the test, runs a series of reactions. These reactions first convert the virus’s ribonucleic acid (RNA), if present, into deoxyribonucleic acid (DNA) and then amplify it (make millions of copies of the DNA); the test then detects this DNA. By running multiple amplification cycles, a PCR test can sense

even low levels of viral genetic material in a patient’s sample, so these tests tend to be highly sensitive (especially traditional laboratory PCR tests).

- A PCR test can be authorized to run batched or “pooled” patient samples if the developer demonstrates that the test meets the EUA standard for pooled testing. If a pooled sample tests positive, the samples that were combined then need to be tested individually to identify the positive case(s). When there is a low prevalence of cases (and a high number of negative results is therefore expected), pooling samples may result in fewer tests needing to be run and fewer testing supplies being required.

2. An **antigen test** detects one or more specific proteins from a virus particle. Most currently-authorized antigen tests are POC tests and provide results in less than an hour. Antigen tests tend to be highly specific but are typically less sensitive than molecular tests. However, because antigen tests can generally be produced at a lower cost than molecular tests and have a simpler design, antigen tests could scale to test millions of individuals per day.

### Authorized uses and conditions of authorization

When authorizing a product for emergency use, the FDA issues a **Letter of Authorization**.<sup>3</sup> Each Letter of

<sup>3</sup> <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas>

Authorization issued for a COVID-19 product is available on FDA's website. These letters set forth the terms and conditions of authorization, including the setting for conducting the test, the indications for using the test, and the responsibilities of the test's developer, distributors, and laboratories performing the test.

### Traditional laboratory versus point-of-care tests versus at-home tests

The vast majority of SARS-CoV-2 diagnostic tests with EUAs are authorized for use in traditional **laboratories** certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 41 U.S.C. §263a, to perform high or moderate complexity tests. Laboratory tests include some tests for which an individual's nasal swab or saliva sample can be self-collected at home and then mailed to an authorized laboratory for analysis. These "home collection" tests may be prescription or non-prescription (direct-to-consumer (DTC)), which will be indicated in the authorization. Laboratory tests are authorized either for the specific laboratory in which the test was developed or for any laboratory that meets certain requirements set forth in the EUA.

Several SARS-CoV-2 diagnostic tests are authorized to be conducted entirely at the point-of-care (POC) without a sample being sent to a separate laboratory for analysis. The term "point-of-care" refers to a patient care setting, such as any of the following that meets certain requirements under CLIA:

- Doctors' offices
- Nursing homes
- Urgent care centers
- Pharmacies
- School nurse offices
- Workplace health clinics

For POC tests, each test authorized to date has been authorized for use in patient care settings operating with a Certificate of Waiver, a Certificate of Compliance, or a Certificate of Accreditation under CLIA. The Centers for Medicare & Medicaid Services (CMS) **issues CLIA Certificates**<sup>4</sup> and enforces compliance with CLIA regulatory requirements.

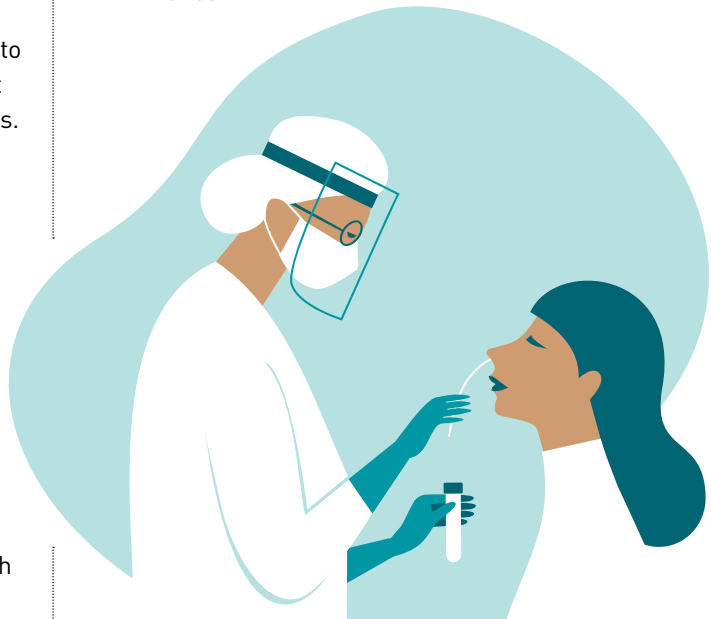
An **at-home** test is a test where a person can collect a sample, test the sample at home, and receive results directly from the test in a short time, such as 30 minutes

or less. Tests authorized to be performed completely at home may be prescription or over-the-counter (OTC), which will be indicated in the authorization. These do not require the individual to send a sample to a laboratory for processing.

### Indications

A SARS-CoV-2 diagnostic test is authorized for use for the specific indications included in the EUA. To assist in the collection and submission of data and information needed to support an EUA request for a test, the FDA has provided templates on the agency's website. The authorized indications for use vary from test to test. For example, a test may be authorized for one of the following categories of indications for use:

- Authorized for use with certain specimen types collected from symptomatic individuals **suspected of having COVID-19 by their health care provider**, provided that the individuals have experienced the onset of **symptoms** of COVID-19 within a pre-specified number of days prior to administration of the test.



- Authorized for use with certain specimen types collected from **individuals who are suspected of having COVID-19 by their health care provider**, even if the individuals lack symptoms of COVID-19.
- Authorized for use with certain specimen types collected from **any individual**, including individuals

<sup>4</sup> <https://www.cms.gov/files/document/laboratory-quick-start-guide-cms-clia-certification.pdf>



without symptoms or any other reasons to suspect COVID-19 infection. Tests with this authorization are referred to as tests authorized for use in “asymptomatic screening.”

### Screening Asymptomatic Patients

For licensed health care practitioners who are prescribing or administering an authorized SARS-CoV-2 diagnostic test for asymptomatic individuals in congregate facilities who are not suspected of having COVID-19, we recommend they consider the information below, as well as the HHS guidance on [PREP Act coverage](https://www.hhs.gov/sites/default/files/prep-act-coverage-for-screening-in-congregate-settings.pdf).<sup>5</sup>

Although the current available literature suggests that symptomatic individuals with COVID-19 and asymptomatic individuals without known exposure may have similar levels of viral genetic material, there is limited data on the distribution of viral loads in individuals with and without symptoms across demographics, different settings, and specimen types.

Therefore, when screening asymptomatic individuals, health care providers should consider using a highly sensitive test, especially if rapid turnaround times are available. If highly sensitive tests are not feasible, or if turnaround times are prolonged, health care providers

may consider use of less sensitive POC tests, even if they are not specifically authorized for this indication (commonly referred to as “off-label”). For congregate care settings, like nursing homes or similar settings, repeated use of rapid POC testing may be superior for overall infection control compared to less frequent, highly sensitive tests with prolonged turnaround times.

When using tests for general asymptomatic screening, health care providers should be aware of the performance of the tests and may want to consider different testing approaches, such as a predefined serial testing plan or directed testing of high-risk individuals.

“Negative” results should be considered as “presumptive negative,” and health care providers should consider them in the context of clinical observations, patient history, and epidemiological information. Thus, if there is a significant new outbreak in a congregate care facility or high clinical suspicion of an infection in an individual resident, a negative POC test should be confirmed with a highly sensitive molecular test (refer to CDC guidelines).

It is not necessary to perform confirmatory high sensitivity molecular tests on individuals with negative antigen test or other POC test results if they are obtained during routine screening or surveillance.

<sup>5</sup> <https://www.hhs.gov/sites/default/files/prep-act-coverage-for-screening-in-congregate-settings.pdf>