

What types of diagnostic tests exist to detect COVID-19?

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with updated sections on antigen testing

A critical element for combatting the COVID-19 pandemic is to have suitable diagnostic tests available.

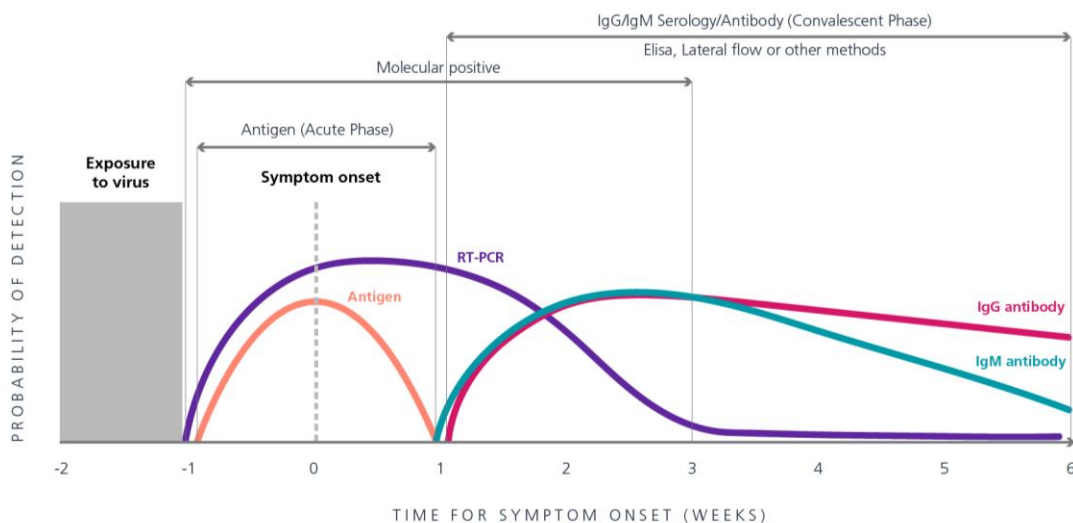
There are generally two different types of tests used to detect the presence of the virus:

- I. **Molecular based COVID-19 tests:** these tests detect the presence of the virus (viral RNA) but do not detect if you have previously been in contact with the virus.
- II. **Antigen detection based COVID-19 tests:** these tests detect the presence of viral antigen (proteins) but do not detect if you have previously been in contact with the virus.

And one type of test used to detect the immune response to the virus:

- III. **Serology tests for COVID-19 (Antibody tests):** these tests detect the immune response against the virus, meaning that the person has previously been in contact with the virus. This test can either be specific to IgG or IgM or measure the addition of all antibodies (TOTAL), including IgA + IgM + IgG

The graph below illustrates the evolution of the various markers (viral RNA, Antigens, Antibodies) of COVID-19. This is based on the typical viral load evolution and patient response based on the present knowledge about SARS-CoV2. Timelines are illustrative and might vary among individuals



Testing of these markers can take place in different settings:

- **Laboratory testing**

Testing that takes place in a specialised laboratory with specific infrastructure, equipment, and trained personnel.

- **Point-of-care (POC) or near-patient testing**

Testing that takes place at the time of the consultation with the results made available in a short time (from few minutes to generally less than one hour). The tests provide immediate information to help make decisions about patient care. Tests can be performed at the bedside or near the patient. In broad terms, POC testing is performed in a healthcare setting that is not the laboratory. These settings can be, for example, in emergency departments, urgent care clinics, general practitioner's offices, or mobile care units. COVID-19 specific locations for POC testing depend on local regulations.

What are rapid tests?

These tests are used singly or in small series and involve simple procedures. Devices validated to run these types of tests have been designed to give a fast result (in less than 1 hour). They may be intended either for use in laboratories or in point-of-care settings.

For laboratory testing and POC testing, all the steps from sampling to interpretation of the result are performed by healthcare professionals.

- **Self-sampling**

Self-sampling implies the possibility for patients to collect the sample themselves. The sample can then be sent to a laboratory for central testing or be tested by the patients themselves, in a case where a test is classified as a self-test.

- **Self-testing**

Self-testing is performed with a device intended to be used by anyone even without formal healthcare or medical experience in their own environment, such as their homes. (e.g. pregnancy test, blood glucose monitoring...). At the time this document was produced, there are very few COVID-19 tests for self-testing and none yet approved for use in Europe.

It is important to mention that the possibility for self-sampling or self-testing depends on local regulations.

I. Molecular based COVID-19 Tests

A. What are molecular based COVID-19 tests?

Molecular based COVID-19 tests work with a sample commonly taken from a person's **nose or back of the throat**. Other potential samples include saliva or bronchoalveolar lavage fluid.

A molecular test is a highly sensitive and specific technique. The tests allow for testing people at an early stage of the infection. They also allow, when performed in laboratories in larger populations, for assumptions about the spread of the virus in a whole population. These tests provide authorities important information for case confirmation and isolation guidance in order to guide measures to protect the people.

B. How do molecular tests work?

The tests look at a specific viral genetic material showing the presence of the virus in the body.

C. Where are these molecular tests performed?

The first step of taking a sample (usually using a nasopharyngeal swab) can be taken anywhere, if the medical staff is well protected by using 'personal protective equipment' (PPEs).

The preparation and analysis of the swabs is usually happening in specialised and approved laboratories by large, immobile molecular machines.

There are also new 'point-of-care' molecular tests. Those can be performed with mobile devices in clinics, doctors' offices, or even mobile drive-in sites.

One main difference between laboratory and point-of-care molecular-tests is the throughput: laboratory tests allow to process hundreds to thousands of samples per day on automated instruments having a footprint of several square meters; point-of-care tests and the corresponding printer-size instruments are suited for running small batches or individual samples at a time.

D. Components and accessories of COVID-19 molecular tests:

- According to the technology used: Nasal, nasopharyngeal (NP) or throat swabs (specific long Q-tip style equipment) or other biological fluid collectors.
- Personal protective equipment for the medical staff taking and processing the swabs
- Dependent on the platform (laboratory-based or point-of-care), additional external reagent may be needed, as extraction reagents.
- Molecular testing reagents including quality controls
- Molecular testing equipment

Combined molecular tests that allow at the same time the detection of COVID-19 and other seasonal respiratory infections have been developed to enable differential diagnostic of these respiratory tract infections.

Increasing demand for testing implies that in addition to scaling up production capacities for tests, third parties' components and accessories are also needed in larger quantities. A shortage of any of these materials would jeopardise the production capacity.

Furthermore, the laboratory capacity, namely the available number of staff and molecular equipment in the territories are another determinant for the number of tests that could be performed at a given amount of time.

II. Antigen based COVID-19 Tests

A. What are antigen based COVID-19 tests?

Diagnostic tests detecting the presence or the absence of proteins of the virus, called antigens.

B. How do antigen based tests work?

The tests detect a specific viral protein material showing the presence of the virus in the body. As for molecular testing, the typical sample is an upper respiratory tract swab (**nose or back of the throat**). Other potential samples include saliva or oral fluid.

Antigens are detectable few days before the onset of symptoms and few days after, overlapping the period in which the patient can transmit viable virus and therefore infect other people. Antigen tests turn negative 5-7 days after the onset of symptoms, whereas molecular testing can remain positive during weeks, even beyond the infectivity period.

C. Where are antigen based tests performed?

These tests can be performed either in the laboratory or at near patient or community care testing. The first versions of the antigen based tests were developed as point-of-care tests. Currently the test is also available in automated high throughput laboratory analysers.

The first step of taking a sample can be done anywhere. The medical staff taking the sample must be well protected with 'personal protective equipment' (PPEs).

The preparation and analysis of the samples depend on local regulations but are usually done by healthcare professionals and can take place on mobile units in emergency wards, clinics and doctors' offices. Alternatively, the samples are transported to laboratories for its automated processing.

One main difference between laboratory and point-of-care antigen tests is the throughput: laboratory tests allow to process hundreds to thousands of samples per day on automated instruments having a footprint of several square meters; point-of-care tests are suited for running small batches or individual samples at a time.

D. Components and accessories of COVID-19 antigen based tests:

- According to the technology used: upper respiratory tract swabs or other biological fluid collectors.
- Personal protective equipment for the medical staff taking the samples
- According to the platform (laboratory-based or point-of-care), additional external reagent may be needed.
- Antigen testing reagents including quality controls
- Antigen testing equipment

III. Serology tests for COVID-19

A. What are serology tests for COVID-19?

Serology tests for COVID-19 generally are performed on blood samples (serum, plasma, or whole blood). The test detects if a person has developed antibodies against SARS-CoV-2. The presence of antibodies and the correlation with acquired immunity, i.e. if a person is protected against a reinfection, is still subject to medical and scientific research at the time of the publication of this paper.

These tests are useful at a later stage of an infection since antibodies need around 5-14 days (IgM and/or IgG) to develop and be detectable in the blood and hence have little diagnostic value. In a few cases when a molecular assay is negative while clinical presentations suggest a potential COVID-19 infection, then serology tests can be used as complementary diagnostic tools.

When performed in large portions of a population, these tests could also provide important information on the diffusion of the infection in the population and could therefore guide authorities in their efforts to ease social distancing measures appropriately.

B. How do serology tests work?

Serology tests, also called antibody tests, come in many different formats and variants. Some immunoassays consist of multiple steps with various reagents being added and washed away or separated at different time points in the assay.

Serology tests detect the presence of antibodies, called IgG and IgM, in the blood. Generally, the presence of IgM only suggests that the person is in the early stage of the infection. Presence of both IgM and IgG (which develop later during the course of infection) suggest that the patient is in a later stage of the disease, whereas IgG only is present during the recovering phase, and should stay positive for months and possibly years depending on the virus. In the case of COVID-19 it has been reported that IgM and IgG concentrations rise practically at the same time.

Some serology tests measure specifically IgG or IgM. Others measure the aggregate of antibodies IgA, IgM and IgG. Measuring the aggregate increases sensitivity, although doesn't differentiate the presence of the different isoforms.

Some serological tests give a qualitative result only (positive or negative) indicating if the person has developed antibodies against the virus or not; others can quantify the level of antibodies which may be correlated with a "level of immunity".

Serology tests will also play a major role in vaccine development. Once vaccination will be available, they might also have an important role in monitoring pre and post vaccinal immunity.

C. Where are these tests performed?

The first step of taking a blood sample can be performed anywhere, if the medical staff is well protected by using 'personal protective equipment' (PPEs).

The preparation and analysis of the blood sample is performed in clinical laboratories on large automated systems.

There are also 'point-of-care' serology tests. Those can be performed with mobile hand-held devices in clinics, doctors' offices or even mobile drive-in sites.

One main difference between laboratory and point-of-care serology tests is the throughput: laboratory tests allow to process hundreds to thousands of samples per day on automated instruments having a footprint of several square meters; point-of-care tests are suited for running small batches or individual samples at a time.

D. Components and accessories of COVID-19 serology tests:

- According to the technology used: lancet or blood sample collectors
- Personal protective equipment for the medical staff taking the blood samples
- According to the platform (laboratory-based or point-of-care), additional external reagent may be needed.
- Serology testing reagents including quality controls
- Serology testing machines

IV. Safety and performance of COVID-19 tests

For all COVID-19 tests, the accuracy level is important. It is defined by its sensitivity (limiting false negatives) and its specificity (limiting false positives). A good sensitivity means no or very few false negative results, a good specificity means no or very few false positive results.

All COVID-19 tests today must adhere to strict regulatory procedures before they get to the market. These laws establish the essential requirements for safety and performance of diagnostic tests. At the same time, market surveillance mechanisms are set-up to ensure that products are further monitored once they are in the market.

It is crucial, more than ever, that requirements and procedures set by the laws are followed. This ensures that reliable and accurate tests are deployed in the battle against the COVID-19 pandemic.

At the same time, COVID-19 tests must be purchased from reliable diagnostic tests producers. It is recommended that prior to purchasing tests, all safety and performance information must be obtained, analysed, and properly taken into account.

V. Summary of Available Tests to Detect COVID-19

	Molecular tests	Antigen tests	Serology tests
	<ul style="list-style-type: none"> • Detect presence of virus 	<ul style="list-style-type: none"> • Detect presence of virus 	<ul style="list-style-type: none"> • Detect immune response to virus
Sample collection	<ul style="list-style-type: none"> • Nasal / Nosopharyngeal / throat swab or other different sample types (e.g. bronchoalveolar lavage fluid, saliva) 	<ul style="list-style-type: none"> • Nasal / Nosopharyngeal / throat swab or other different sample types (e.g. bronchoalveolar lavage fluid, saliva) 	<ul style="list-style-type: none"> • Blood samples (venous, capillary or serum/plasma)
Detection	<ul style="list-style-type: none"> • Zoom in on genetic signature of the virus (RNA) 	<ul style="list-style-type: none"> • Detect presence of proteins of the virus (antigens) 	<ul style="list-style-type: none"> • Detect if person has developed antibodies
What these tests say	<ul style="list-style-type: none"> • Detect <u>current or recent</u> COVID-19 infection 	<ul style="list-style-type: none"> • Detect <u>current</u> COVID-19 infection 	<ul style="list-style-type: none"> • Detect <u>previous contact</u> with COVID-19
Why it is helpful	<ul style="list-style-type: none"> • Molecular tests are highly sensitive and specific • Allow for testing people at an early stage of the infection • Can inform on the spread of the virus • Provide relevant information for case confirmation and isolation guidance 	<ul style="list-style-type: none"> • Can be done from point of care to centralized testing in automated laboratories • High sensitivity only in the period of infectiousness, allowing to quarantine only infectious individuals 	<ul style="list-style-type: none"> • Provide important information on diffusion of infection for large portions of populations • Will play a major role in vaccine development, inc. monitoring pre / post vaccinal immunity
Where these tests are performed	<ul style="list-style-type: none"> • First sample taken anywhere • New point-of-care with mobile devices e.g. clinics, doctors' offices, mobile drive-in sites • Preparation / analysis happens in laboratories • Laboratories can run larger batches (thousands per day) than point-of-care 	<ul style="list-style-type: none"> • First sample taken anywhere • New point-of-care with mobile devices e.g. clinics, doctors' offices, mobile drive-in sites • Preparation / analysis depend on local regulations • Laboratories can run larger batches (thousands per day) than point-of-care 	<ul style="list-style-type: none"> • First sample taken anywhere • Point-of-care tests with mobile hand-held devices in clinics, doctors' offices or even mobile drive-in sites • Preparation / analysis done in clinical labs on large automated systems • Laboratory tests can run large batches (thousands per day) when compared to point-of care capacity

<p>Components / accessories</p>	<ul style="list-style-type: none"> • Upper respiratory tract swabs or other biological fluid collectors • Personal protective equipment for medical staff • Additional external reagent may be needed depending on platform (lab or point-of-care) • Molecular testing reagents including quality controls • Molecular testing equipment 	<ul style="list-style-type: none"> • Upper respiratory tract swabs or other biological fluid collectors • Personal protective equipment • Additional external reagent may be needed depending on platform (lab or point-of-care) • Antigen testing reagents including quality controls • Antigen testing equipment 	<ul style="list-style-type: none"> • Lancet or blood sample collectors • Personal protective equipment • Additional external reagent may be needed depending on platform (lab or point-of-care) • Serology testing reagents including quality controls • Serology testing machines
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