NCDHHS Provider Guidance on SARS-CoV-2 Testing

Outline of Contents

1: Overview of Available SARS-CoV-2 Testing Modalities

There are currently two types of tests for SARS-CoV-2: diagnostic and antibody.

A: Diagnostic Testing

Testing Modalities

- Molecular (RT-PCR) tests that detect the virus's genetic material (RNA)
- Antigen tests that detect specific proteins on the surface of the virus

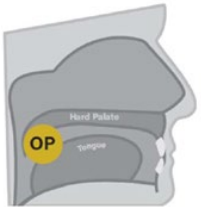
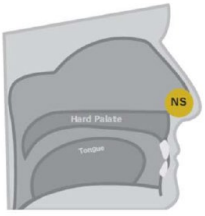
Indications for Use

Diagnostic tests should be used when active viral infection is suspected, either because the patient is symptomatic and/or they have been in close contact (within 6 feet for 15 minutes or more) with someone with confirmed COVID-19 diagnosis, regardless of symptoms.

Sample Collection

Both molecular and antigen tests currently require nasal or throat swabs. Saliva and cheek swab tests may come to market in the future but are not currently available for use in North Carolina.

For self-collected samples (mid-turbinate and nasal), it is important to ensure the quality of the sample by instructing the patient on how to collect the sample properly.

	Nasopharyngeal (NP)	Oropharyngeal (OP)	Mid-Turbinate	Nasal
Location				
Pros	▪ Ideal sample – most sensitive	▪ More sensitive than Mid-Turbinate or Nasal	▪ Requires less PPE ▪ Can be self-collected	▪ Requires less PPE ▪ Can be self-collected ▪ Strong supply of foam, flocked or poly swab
Cons	▪ Requires most PPE ▪ Very limited supply of special flocked swab	▪ Requires most PPE ▪ Very limited supply of special flocked swab ▪ Less sensitive than NP	▪ Very limited supply of special flocked swab ▪ Less sensitive than NP or OP	▪ Least sensitive location for sample collection

To request bulk specimen collection materials through an online portal managed by NCDHHS: https://covid19.ncdhhs.gov/information/health-care/requesting-specimen-collection-supplies.

Check with your lab to determine compatibility with NCDHHS swab types and viral transport medium.

Testing Process and Characteristics

	Overview	Interpreting Results
Molecular Test: Lab-based	▪ Widely available ▪ Highly sensitive ▪ Highly specific ▪ Can take several hours to days for result ▪ High throughput	Positive: Patient most likely has active SARS-CoV-2 infection and should isolate immediately. Negative: Patient most likely does not have active SARS-CoV-2 infection.
Molecular Test: Point-of-Care	▪ Few options currently authorized for use by FDA ▪ Less sensitive – should only be used for symptomatic patients ▪ Highly specific ▪ Fast result but low throughput	Positive: Patient most likely has active SARS-CoV-2 infection and should isolate immediately. Negative: If highly suspect SARS-CoV-2 infection, recommend ordering lab-based PCR test due to possible false-negative result.
Antigen Test: Point-of-Care	▪ Few options currently authorized for use by FDA ▪ Less sensitive – should only be used for symptomatic patients ▪ Highly specific ▪ Fast result but low throughput	Positive: Patient most likely has active SARS-CoV-2 infection and should isolate immediately. Negative: If highly suspect SARS-CoV-2 infection, recommend ordering lab-based PCR test due to possible false-negative result.

Reporting Results

Effective February 3, 2020, physicians and laboratories in North Carolina are required to immediately report suspected or confirmed cases of novel coronavirus infection to state or local health departments via telephone or facsimile of basic contact information of the case.

Effective July 7, 2020, physicians, laboratories, and other providers ordering and conducting diagnostic testing for COVID-19 in North Carolina must report all COVID-19 diagnostic test results, both positive and negative. This includes all viral tests and does not include antibody tests. Refer to the State Health Director temporary order on diagnostic testing for further details on required reporting elements.

July 7 State Health Director Temporary Order: https://files.nc.gov/covid/documents/guidance/healthcare/SHD-Order-Guidance-SL-2020-4-Sec.4.10.a.pdf.

B: Antibody Testing

Indications for Use

Antibody tests should not be used to diagnose active SARS-CoV-2 infection, especially for patients who have had an onset of COVID-19 symptoms in the past 7 days. In a case of long-standing symptoms of COVID-19 (defined as greater than 9 days), antibody testing may be used as one piece of clinical evidence in the confirmation of infection with SARS-CoV-2. This can be useful if PCR based testing is negative, showing an absence of detectable virus, or unavailable. Antibody testing may also be useful in patients presenting with late-stage complications of COVID-19, such as multisystem inflammatory syndrome in children.

Sample Collection

Sample collection for antibody testing is either a blood draw or finger stick, depending on the type of test being used for processing.

Testing Process and Characteristics

Antibody tests cannot determine a person's immunity to reinfection with SARS-CoV-2 and should not be used as an "immunity voucher" for work or daycare in an attempt to assure the safety of individuals.

	Overview	Interpreting Results
Rapid Diagnostics Tests	▪ Low throughput ▪ Lowest sensitivity ▪ Lower specificity than other platforms ▪ More costly but do not require specialized expertise to perform	*Assuming 5% pre-test probability (prevalence) and best test case:* Positive Predictive Value: 82.9% Negative Predictive Value: 99.4%
Chemiluminescent Immunoassays	▪ High throughput ▪ Highest sensitivity ▪ Highest specificity ▪ Highest precision ▪ Require specialized lab expertise to perform	*Assuming 5% pre-test probability (prevalence) and best test case:* Positive Predictive Value: 92.9% Negative Predictive Value: 100%
Enzyme-linked Immunosorbent Assays (ELISA)	▪ Low throughput ▪ Highest sensitivity ▪ Highest specificity ▪ Highest precision ▪ Require specialized lab expertise to perform	*Assuming 5% pre-test probability (prevalence) and best test case:* Positive Predictive Value: 91.7% Negative Predictive Value: 99.6%

See below for adjusting your estimate of the likelihood your patient has COVID depending on your pretest estimate and the characteristics of the test you are using.

Reporting Results

Currently, positive antibody results do not need to be reported to the Local Health Department.

Additional Resources

IDSA COVID-19 Antibody Testing Primer: https://www.idsociety.org/globalassets/idsa/public-health/covid-19/idsa-covid-19-antibody-testing-primer.pdf

2: FDA Testing Overview

https://www.fda.gov/consumers/consumer-updates/coronavirus-testing-basics

Different Types of Coronavirus Tests

	Molecular Test	Antigen Test	Antibody Test
Also known as...	Diagnostic test, viral test, molecular test, nucleic acid amplification tests (NAAT), RT-PCR tests	Rapid diagnostic test (Some molecular tests are also rapid tests.)	Serological test, serology, blood test, serology test
How the sample is taken...	Nasal or throat swab (most tests) Saliva (a few tests)	Nasal or throat swab	Finger stick or blood draw
How long it takes to get results...	Same day (some locations) or up to a week	One hour or less	Same day (many locations) or 1-3 days
Is another test needed...	This test is typically highly accurate and usually does not need to be repeated.	Positive results are usually highly accurate but negative results may need to be confirmed with a molecular test.	Sometimes a second antibody test is needed for accurate results.
What it shows...	Diagnoses active coronavirus infection	Diagnoses active coronavirus infection	Shows if you've been infected by coronavirus in the past
What it can't do...	Show if you ever had COVID-19 or were infected with the coronavirus in the past	Definitively rule out active coronavirus infection. Antigen tests are more likely to miss an active coronavirus infection compared to molecular tests. Your health care provider may order a molecular test if your antigen test shows a negative result but you have symptoms of COVID-19.	Diagnose active coronavirus infection at the time of the test or show that you do not have COVID-19

3: Pre- and Post-Test Probability: Answering the Question "What Are the Chances of My Patient Actually Having (or Not Having) COVID-19 After Testing?"

As you're evaluating your patient and using diagnostic tools to determine a possible SARS-CoV-2 infection, it is important to consider the **pre- and post-test probability** in concert with the sensitivity and specificity of the particular test you are using in order to reach a more accurate diagnosis.

Taking into consideration your patient's likelihood of COVID-19 based on symptoms, exposure history, estimate their pre-test probability. Some examples and guidance below.

What is the likelihood of a patient having COVID after testing? To estimate this, a clinician needs to estimate the likelihood of disease based on clinical presentation and then calculate (or if you are smart and efficient, use an online calculator) the probability of disease. This one is simple and easy to use: http://getthediagnosis.org/calculator.htm.

The probability of disease after any given test depends upon both the pretest probability of disease and the accuracy of the test (its sensitivity and specificity).

1. How do I estimate the pretest probability? For COVID-19, there is no tool like the Well's criteria for pulmonary embolism so one must use some basic understanding of the epidemiology along with your clinical skills. In North Carolina, approximately 6% of those undergoing testing have COVID-19. The overall prevalence of all North Carolinians is unknown though thought to be quite a bit lower.
    - If you feel your patient's risk is about average for all tested individuals, go ahead and use a 6% pretest probability.
    - If you have a lower risk patient such as an individual who had a brief exposure 1 week ago though no current symptoms, you might lower that risk to 2% or so.
    - Let's imagine you have a patient at somewhat higher risk. Imagine a woman with both mild cough and fever and a likely risky exposure, then you might use a pretest probability of 25%.
    - If the patient is very high risk such as someone with a close work contact known to be positive and your patient has typical signs and symptoms such as loss of smell, high fever, myalgias, and cough, you might use a pretest probability of 75%.
2. To calculate the probability after testing, you need to know the accuracy of your lab's testing. Most RNA tests, the most commonly used type, are highly specific at around 99%. This means the test will be negative in individuals who don't have COVID 99% of the time. This is the true negative rate. Sensitivity, or true positive rate, varies more though is typically 95% or so. Best to check with your lab though some examples are listed in the table below.
    - Antigen tests produce results more quickly though have significantly lower sensitivity (true positive rate), approximately 80-85%. The specificity (true negative rate) is nearly as high as RNA tests, about 98%. This information means a positive test is likely true while a clinician should have less confidence in a negative test as it has a higher possibility of being a false negative (patient has COVID, test failed to detect it).

- Test accuracy is best determined on clinical specimens rather than "spiked specimens" that test manufacturers may choose to report. Here are a few published figures:

Test Name	Sensitivity (TPR)	Specificity (TNR)
ID NOW COVID-19 – PCR	95%	98%
Sofia 2 SARS Antigen FIA	80%	100%
RealStar® SARS-CoV-2 RT-PCR Kit	92%	100%

- For practice, let's consider that all 4 of our above theoretical patients with varying pre-test probabilities are tested. The table below shows how we should estimate the patient's probability of having COVID if the NOW COVID-19-PCR test is + or -. All were calculated using http://getthediagnosis.org/calculator.htm.

Example patients and their pretest probability	Positive Test	Negative Test
Lucy Low Risk (no sx, brief exposure) 2%	49%	0%
Joe Average 6%	75%	0%
Maria Moderate (cough, likely exposure) 25%	94%	2%
Bob Lookin' Bad (lots of sx, close exposure) 75%	99%	13%

So you can feel fairly confident recommending isolation after a positive test for the last 3 and a negative test for the first 3. What about Bob Lookin' Bad if he tests negative? 13% may be too high to send him back to his job as a CNA in a nursing home. What to do? Order another, more **sensitive** test-ideally one with near 100% sensitivity. If negative, you then have ruled out COVID. For a great tool to get a better feel visually for yourself or anyone you want to show check out this NEJM piece. The "Interactive Graphic" right on top demonstrates how important pretest probability and test sensitivity are in reaching a conclusion that our patient does not have COVID-19.

4: Evaluating POC (Point of Care) COVID-19 Testing for In-Office Use

There are many tests currently on the market that can be used for COVID-19 testing. The landscape can be overwhelming and confusing. This guide is designed to help medical providers make better decisions when considering buying a testing platform or adding to your current testing platform for your office.

- If you are currently using a testing platform, consider finding out from the manufacturer if they provide a test kit or add-on for COVID-19 for your current system.
- If you are contemplating buying a new system, realize most systems require that your lab meet the requirements for "moderate complexity" under CLIA regulations.
- If you don't meet those requirements, you will only be able to add COVID-19 testing that is considered "waived."

A: COVID-19 Lab Test Evaluation Question List

For those wanting to start POC testing for COVID-19.

B: The Basics

1. Confirm whether the test you are considering can be used in:
    a. A CLIA "Waived" laboratory
    b. A CLIA Moderate complexity laboratory

    If you are operating under a CLIA Certificate of Waiver, and wish to add a non-waived method, you will need to "upgrade" your CLIA certificate and meet additional regulatory requirements.
2. What is the test's sensitivity? Sensitivity is the TRUE POSITIVE RATE. Sensitivity refers to a test's ability to correctly identify an individual *with* the disease by returning a positive result. A highly sensitive test means that there are few false negative results, and thus fewer cases of disease are missed.
3. What is the test's specificity? Specificity is the TRUE NEGATIVE RATE. Specificity refers to the ability of the test to correctly identify those *without* the disease. A highly specific test means that there are few false positive results.

Sensitivity and specificity are *not dependent upon* the disease prevalence rate.

C: Questions to Ask the Manufacturer Regarding Their Validation of the Test

4. How many samples were used in your validation of the test? More is better.
5. Has the test been used in any clinical trials? This might improve confidence in the test.
6. Is your company continuing to perform validation studies since test release? They should be.
7. What is the source of the control samples? Did you use clinical samples from patients, or did you use 'spiked' (that is, COVID-19 remnants or dead virus added to the controls) samples?

Please note: Use of clinical samples is generally better as there will be more variability in them than with spiked samples.

8. If you used clinical samples, did the positive test population have symptoms in addition to a positive PCR test? This improves the validation of a positive test.
9. For the negative test group, were pre-pandemic samples used as controls? This assures you are not adding a false negative into the system.
10. Were there tests to determine cross-reactivity (other forms of coronaviruses) and specificity for other viruses? What was the result?

D: Other Questions to Ask the Manufacturer

11. If considering adding an antibody test, ask the manufacturer when their validation samples were collected in relation to a positive viral RNA test.
12. Ask about total cost. In addition to the testing platform, what are the costs of any reagents, special swabs, other parts of the test kits, etc. that you will be needing to purchase on a regular basis.
13. What would be the average cost per kit including everything?
14. Are they working on new tests (neutralizing antibodies) or sample types (saliva) that will be added to the platform? Will there be any additional cost for adapting the new product?
15. What is the wait time before receiving the testing platform?
16. Has the manufacturer had supply chain issues getting components for the test kits?
17. Does this test require one specific swab or transport medium, or are there alternatives that can be substituted in case of supply delays?
18. Where are the kits manufactured? What about other components or reagents?
19. What kind of training and support are needed? Is testing support included in the price?