Returning to daily life responsibly

An informed strategy for comprehensive COVID-19 testing.

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Introduction

Over the past year, **SARS-CoV-2** (COVID-19) has challenged nations and the global medical establishment. Although most people infected by the virus are **symptomatic**, many remain **asymptomatic** and unaware that they are contagious. This characteristic, compounded by a long window of **viral shedding**, makes controlling COVID-19 a difficult challenge for public safety and economic health.

In response, the Centers for Disease Control and Prevention (CDC) established the following protocols to lessen the spread of the virus and to help protect people at increased risk of severe illness:

- social distancing[1]
- wearing a mask when social distancing is not possible[1]
- avoiding crowds and indoor occupied spaces[1]
- washing or sanitizing hands frequently[1]

Glossary

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, the virus that causes Coronavirus Disease 2019 (COVID-19).

Symptomatic: Having symptoms. With COVID-19, examples of symptoms could be cough, fever, and shortness of breath.

Asymptomatic: Not having symptoms.

Viral shedding: When a virus replicates inside the body and is released into the environment.

Even with the CDC measures, intermittent lockdowns, and quarantine practices, over 500,000 Americans had died from COVID-19 by the end of February 2021.[2] The greatest loss of life is among the elderly, individuals with underlying medical conditions, people of color, and the economically disadvantaged. To help mitigate the impact of the pandemic, expansive laboratory testing protocols have been put in place to help further control the spread of COVID-19.

On November 11, 2020, American Clinical Laboratory Association (ACLA) member laboratories collectively performed 495,000 COVID-19 PCR tests in a single day.[3] But many labs face challenges that stress testing ability. For example, demand for testing after the holidays exceeded the testing capacity of some clinical labs and threatened the turnaround time of results.

It is important to have a testing strategy in place so demands can be met. An optimal strategy requires:

1. Understanding of the types of testing available
2. Using the right test for the right person at the right time
3. Flexibility to make ongoing adjustments in rapidly changing conditions

This white paper seeks to explain the impact that a proactive, comprehensive, and diverse testing strategy can have on protecting individual and population health while minimizing the economic impact of the pandemic. With this basic knowledge, policymakers will be better equipped to design optimal diagnostic, screening, and surveillance programs that leverage all available laboratory assets.

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A comprehensive testing strategy

Tests for SARS-CoV-2 (COVID-19) serve three clinical objectives: diagnosis, screening, and surveillance.[4] Each objective is necessary to help control infection spread.

Diagnosis

This helps positively identify an infected person and control transmission. Scenarios where diagnostic testing is used include:

- Individuals showing symptoms consistent with COVID-19
- Asymptomatic individuals with recent known or suspected exposure to COVID-19

Screening

This helps identify the likelihood someone may have COVID-19. Because 20%[5] to 45%[6] of infections are asymptomatic, screening is essential to identify infection early and help prevent spread. Scenarios where screening is used include:

- Asymptomatic individuals without known or suspected exposure to coronavirus
- Testing to determine resolution of infection (e.g., earlier discontinuation of home isolation at day 7)[7]

Surveillance

This helps observe COVID-19 spread at a large scale. A scenario where surveillance is used is:

- Population-based cohort testing designed to detect possible prevalence of COVID-19

Example Scenarios

- **Diagnosis scenario 1:** A person has developed a fever and cough and lost his sense of smell. Because of these symptoms, he takes a diagnostic test to find out if he is positive for COVID-19.
- **Diagnosis scenario 2:** A person finds out a coworker they work closely with has COVID-19. While she doesn't have symptoms, she takes a diagnostic test because of this exposure and possibility of asymptomatic infection.
- **Screening scenario 1:** A person with no known exposure or symptoms takes a screening test before getting on an airplane to determine the likelihood he has COVID-19 and if he can travel.
- **Screening scenario 2:** A person has been isolating at home after getting COVID-19. She takes a screening test to determine the likelihood she no longer has COVID-19.
- **Surveillance scenario:** Volunteers participate in a surveillance study to help public health officials determine the true prevalence of COVID-19 in their community.

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Testing capabilities

There are two broad categories of COVID-19 tests:

1. **Diagnostic tests:** Tests that can identify a current infection. There are two types of COVID-19 diagnostic tests: PCR* and antigen.
2. **Antibody tests:** Also known as serology tests, these tests detect the presence of antibodies to indicate a previous infection.

When selecting a test for use, the method, turnaround time, performance and accuracy, as well as limitations of each test must be considered (see Table 1. Characteristics of COVID-19 Tests). The following sections describe these testing capabilities in greater depth.

*PCR is one of several types of molecular tests to detect SARS-CoV-2 RNA that have received FDA Emergency Use Authorization (EUA).

Glossary

Sensitivity: The ability of a test to correctly identify patients with a disease. A high sensitivity means the test is accurately identifying patients who are infected (true positive).

Specificity: The ability of a test to correctly identify patients who do not have the disease. A high specificity means the test is accurately identifying patients who are not infected (true negative).

False-negative: A person who tests negative, but actually does have the disease.

False-positive: A person who tests positive, but actually does not have the disease.

Point-of-care testing: Testing at the place of patient care; also known as near-patient testing (ex: the doctor's office).

Table 1. Characteristics of COVID-19 Tests[8-10]

	Diagnostic		Antibody
	PCR Test	**Antigen Test**	**Antibody Test**
What can it do?	Shows a current coronavirus infection. Antigen tests are more likely to miss COVID-19 infections in early phases; therefore, more frequent testing is needed compared to PCR tests. Due to lower sensitivity, CDC recommendation is to perform a PCR test if an antigen test is negative in a symptomatic patient.		Shows a previous coronavirus infection. Antibody tests may identify a potential immune response to a recent or prior COVID-19 infection or vaccine.
How is the sample taken?	Nasopharyngeal (the part of the throat behind the nose), anterior nares (nasal) or throat swab / saliva	Anterior nares or nasopharyngeal swab	Finger stick or blood draw
How long does it take to get results?	Same day to 1 week (depending on location)	Some may be very fast (15–30 minutes)	Same day to 3 days (depending on location)
What is the sensitivity and specificity?	Highly sensitive (especially laboratory PCR tests) and highly specific	Highly specific, but generally less sensitive than PCR tests	Sensitivity and specificity vary by type of test used
Is another test needed?	This test is typically highly accurate and usually does not need to be repeated if positive.	A PCR test is needed if antigen test results are not consistent with the individual's symptom status and/or exposure risk.	Semi-quantitative antibody tests can measure antibody levels to reveal changes in an individual's immune response over time.

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Diagnostic tests

A diagnostic test, also known as a viral test, can identify a current coronavirus infection and be used to recommend immediate quarantine from others. The two types of diagnostic tests are PCR and antigen.

PCR (molecular) testing

Molecular tests detect RNA genetic material from the virus to determine if a person is infected. PCR tests using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) are the most common molecular test. Other COVID-19 molecular tests include transcription-mediated amplification (TMA) and loop-mediated isothermal amplification (LAMP) assays, which are collectively addressed as nucleic acid amplification tests (NAAT).

Pros:

- Considered the gold standard for COVID-19 diagnosis[11,12]
- Have a high **sensitivity** and therefore unlikely to return **false-negative** results

Cons:

- Expensive—a single test kit could cost more than $100 USD due to the resources and logistics required
- Slower because most are performed in a laboratory, not at the **point of care**[13,14]
- Less accurate at detecting COVID-19 during later stages of an infection

While PCR testing is ideal for accurately diagnosing symptomatic people, this method alone is not ideal to meet the urgency and volume of testing required by this pandemic.

Antigen testing

Antigen tests detect specific proteins from the virus to determine if a person is infected.

Pros:

- Generally more affordable than PCR tests
- Can be done quickly and easily at the point of care (turnaround time of 15-30 minutes for results), making them suitable as a screening measure
- When performed frequently (i.e., every 3–7 days depending on the disease prevalence), cases can be quickly identified in asymptomatic individuals[16]

Cons:

- Less sensitive than PCR tests and may return more false-negative results
- Less accurate at detecting COVID-19 during later stages of an infection

Even with lower sensitivity, frequent antigen testing can be used to quickly identify infected, asymptomatic people so they can be isolated early.

Antigen Testing Case in Point: University of Arizona[15]

In April 2020, the administration of the University of Arizona reported a new approach to detecting COVID-19 infections among asymptomatic students. When they tested wastewater from dormitories, they found SARS-CoV-2 flowing from a particular location. The school applied antigen testing immediately to the building residents, finding two positive, asymptomatic students who were quickly isolated.

This successful use of antigen testing helped reduce the risk that students may spread COVID-19 into other communities, like when traveling home for holidays. As of October 2020, the University of Arizona's efforts have suppressed the university's positivity rate to just 0.07%, which is well below the 5% alarm threshold indicated by the World Health Organization.

Using antigen tests for screening vs. diagnosis

It has been shown that antigen tests can help expand testing capacity by providing faster and generally more affordable screening and diagnostic options.

- **Screening:** Antigen testing can be easily scaled, making it possible to screen large numbers of people. This includes people who are in congregate living settings, at workplaces, and traveling. According to the CDC, rapid antigen tests can be especially helpful for screening in high-risk settings, such as nursing homes, where repeat testing could quickly identify persons with COVID-19, inform infection prevention and control measures, and help prevent transmission.[17]
- **Diagnostic testing:** In situations where PCR testing is not available for diagnosis, antigen testing can be a reliable first-line alternative. However, a confirmatory PCR test is needed if a symptomatic patient receives negative antigen test results, or if an asymptomatic patient receives positive antigen test results.[18] This alternative helps to reduce the strain on laboratories because it frees up PCR testing capacity.

Antibody tests

When a person is infected by a virus, the immune system reacts to the threat by producing antibodies that fight the invader. Antibody tests detect the presence of these antibodies in blood after an infection. The current body of research indicates that antibodies to COVID-19 infection can remain for months.[20] Some people are distrustful of antibody tests because there were concerns over accuracy early in the pandemic. Today, antibody tests with demonstrated high specificity (>99%) are widely available, making the test results far more accurate.[21]

Can do:

- Support diagnosis of COVID-19 in late-stage infections (9–14 days after illness onset)[22]
- Help identify disproportionately impacted populations, such as African American, Hispanic, and Native American communities[23]
- Identify people with antibodies who may not need ongoing screening to help prioritize the use of antigen and PCR testing resources and make testing programs more scalable and affordable
- Provide confirmation of a prior COVID-19 infection. With the growing evidence of long-term health effects, such as lung damage,[24] this gives doctors valuable information to guide an individual's future care.
- Help prioritize vaccine distribution by identifying the most vulnerable individuals

Can't do:

- *Cannot* be used for primary diagnosis

Antibody Testing Case in Point: The REACT Program[19]

Over 365,000 people across England participated in the largest documented antibody home surveillance study for COVID-19. The REACT program, led by Imperial College London, provided insights into antibody response over time. Specifically, people who did not show symptoms of COVID-19 were likely to lose detectable antibodies sooner than symptomatic individuals, and the loss of antibodies was slower in younger people as compared to those aged 75 and over.

In light of their findings, the study authors point to a clear mandate that regardless of the result of an antibody test, compliance with government guidelines including social distancing, self-isolating, and getting tested when symptomatic is essential to controlling the spread of the virus.

CDC studies suggest that nationwide, the actual number of infections may be 6–24 times more than reported cases.[25] Antibody testing captures prior infections to show a more complete picture of community infection and inform effective public health policies. Testing can also help estimate how much of the population has not yet been infected, enabling public health officials to better plan for future healthcare needs.[26]

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Conclusion

Current measures and practices, like social distancing, mask wearing, and handwashing, help to prevent the spread of COVID-19. However, we also need to use a comprehensive testing strategy that includes PCR, antigen, and antibody testing to get back to daily life responsibly. These tests can work together to provide the diagnosis, screening, and surveillance needed to identify COVID-19 infections early and effectively, keep labs ahead of demand, and help guide policymaking decisions.

At the close of 2020, COVID-19 cases were again rising across the United States. It is imperative that we contain the spread of SARS-CoV-2. Yet we must do so while enabling America's workforce and students to safely return to work and studies, so that critical industries and institutions can survive. Carefully designed strategic testing presents a clear path out of the pandemic and can effectively address the current crisis until vaccines are widely administered. Indeed, testing will continue to play a pivotal role in prioritizing the vaccination of the American people.

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