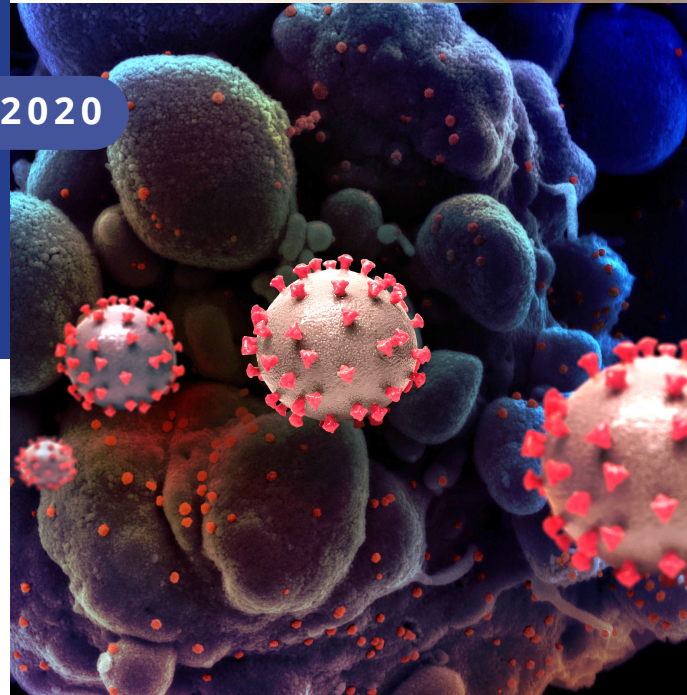
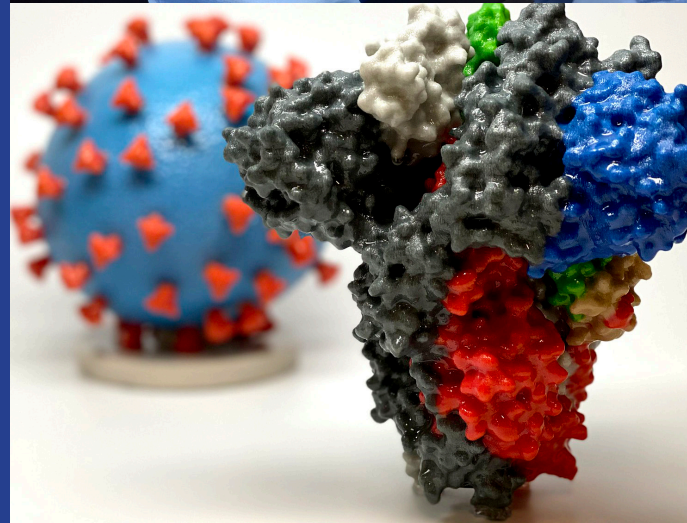
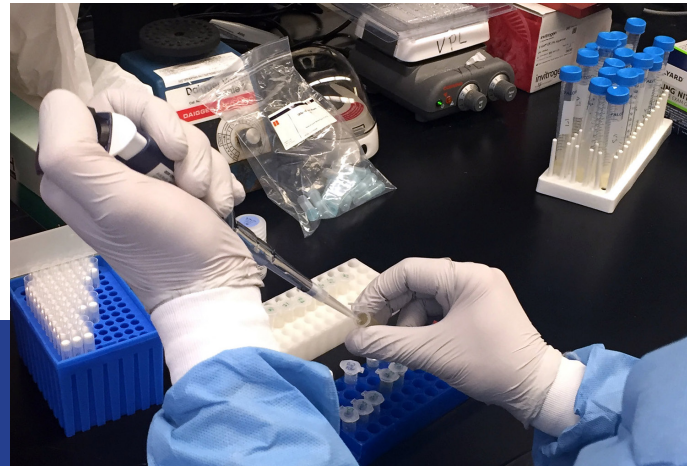
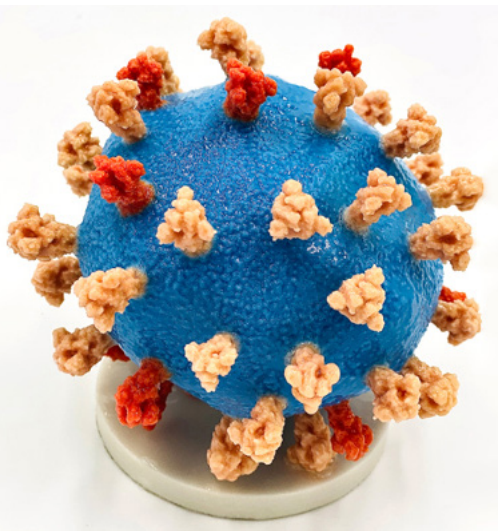


## FROM DEVELOPMENT TO MARKET: UNDERSTANDING COVID-19 TESTING AND ITS CHALLENGES

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## Authors

Monika Schneider, Managing Associate  
Susan Dentzer, Senior Policy Fellow  
Sarah Sheehan, Research Associate  
Karley Whelan, Research Assistant  
Christina Silcox, Managing Associate  
Marianne Hamilton Lopez, Research Director  
Marta Wosińska, Deputy Director  
Mark McClellan, Director

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## Executive Summary

Amid the SARS-CoV-2 pandemic and a crisis over inadequate and delayed testing, this paper describes COVID-19 testing methods and applications, the regulatory process for approving tests, how tests are paid for, and how access to testing is obtained. The paper also highlights the challenges that stakeholders are facing, and will face, in the coming months around COVID-19 testing. It is intended to assist employers, local, state, and federal officials in addressing the testing crisis by enabling more informed planning and test deployment.

The SARS-CoV-2 global pandemic has demonstrated the importance of diagnostic testing and disease tracing as a strategy for containing viral transmission and safely reopening schools and workplaces. This strategy can help to slow or halt the cycle of transmission by detecting people who have become infected, quarantining or isolating them, and subsequently identifying others with whom they have been in close contact. Screening and surveillance testing are also used to understand the drivers and dimensions of outbreaks. Despite some concerns that the spread of the virus in some communities has been so extensive as to have made testing irrelevant, it is still the case that widespread screening tests will be needed to make critical decisions about reopening businesses and returning to work and schools.

Tests are used for the purposes of diagnosis, screening, and surveillance, and there are three types of tests that can be employed for each. There are tests that use samples from patients' respiratory tracts to identify active infection in the body by detecting either genetic material or specific viral proteins: "molecular" and "antigen" tests, respectively, which are used for diagnosis and screening. In contrast, "serology tests" use patients' blood samples to look for antibodies that indicate whether a person was infected in the past, and this information contributes to surveillance.

Development, delivery, and scaling of these testing methods has been and will continue to be very challenging, for multiple reasons. Although a number of developers are producing needed tests and supplies to address this crisis, testing availability, testing supplies, and test processing capacity in the United States are still not at all sufficient to meet growing demand. What's more, not all test products are of the same quality or accuracy, so guidelines on standards and limitations of different tests need to be better understood. And because accurate test results must be communicated to all those who need the information, it is critical to address the gaps in the healthcare and public health data ecosystem.

A number of other key issues around testing remain unresolved, such as how much diagnostic and screening testing the nation should aim to conduct daily, and therefore how much testing capacity is needed; how to employ testing protocols for asymptomatic individuals, such as employees in work sites or students at K-12 schools and universities; who or what entities should bear the large costs of testing; and, given the substantial delays that persist in test processing, how that process can be executed more efficiently. It is urgent that policy makers come to grips with these issues and shape new approaches at the local, state, and national level.

Coordination and cooperation will be needed among a number of stakeholders to resolve these issues and ensure effective deployment of COVID-19 testing strategies. Strategies that reward product and process innovation, expand access, and induce appropriate application of tests are critical to weather the crisis now and into the future.

This paper identifies the following issues as critical for improving the nation's testing response:

1. **A far more robust federal strategy for coordination of testing protocols and resources, as well as data standards, is needed.** In the absence of a directive articulating a federal testing approach, states and localities will continue to have lead responsibility for testing strategies, including developing frameworks to guide frequency of testing and prioritization guidelines. In addition, stronger federal efforts to procure, and possibly to facilitate production of, testing supplies are needed as shortages of testing components continue in pockets across the country.
2. **Specific testing strategies will need to be adjusted based on population and location** to ensure rapid expansion of capacity and faster turnaround times to results. Policymakers should consider a number of factors in their strategies, including disease prevalence, needed time to results, reliability of results, and feasibility of employing rapid screening or pooled testing in certain contexts.
3. Reliable data reporting is critical to assess outbreaks, progress, and distribution of resources, but **additional efforts are needed at the federal and state levels to ensure consistency in data components and information transfer.** In addition, as resources shift to rapid testing, stakeholders need to develop plans for reporting the results of routine screening tests.
4. Given the large number of tests that will be required for widespread screening and frequent testing of asymptomatic individuals, reimbursement at current rates will become very costly over time, and **new financing mechanisms for testing should be considered.** Future legislation should not only provide funding for testing, but should also address what portion of the cost should be borne by consumers, if any.
5. The science behind asymptomatic infection is still not well understood, and this lack of knowledge has implications for both diagnostic testing and routine screening, especially on whether there will be consistently detectable virus or antibody levels. While the US Food and Drug Administration (FDA) recently added information on how to validate molecular and antigen tests for asymptomatic testing, strategies to efficiently validate tests for routine, repeated screening of asymptomatic individuals should be a priority, which **will require additional resources for research and regulation to ensure that safe and effective tests get to market faster.**



## Introduction

Reports of infections from what appeared to be a novel coronavirus emerged from China in late December 2019. In the following eight months, the virus now termed SARS-CoV-2, for Severe Acute Respiratory Syndrome Coronavirus 2, has caused a global pandemic, with more than 20 million cases and more than 700,000 deaths globally as of publication of this paper. The disease caused by SARS-CoV-2 is termed COVID-19.

The global pandemic caused by SAR-CoV-2 has fundamentally upended work, social, and economic activities. Governments, healthcare systems, and businesses are struggling to contain transmission and find a path to “re-opening” that reduces health risks, especially for essential workers and vulnerable populations. Until an effective preventive treatment is approved, quickly identifying and isolating new cases through testing is a critically important complement to behavioral changes that include physical distancing, wearing masks, and hand washing.

Testing for both active and past infections is critical (see: “Applications of COVID-19 Tests”). Identifying active infections rapidly and ensuring isolation and treatment of that individual is crucial to reducing transmission. Identifying people who have been infected in the past provides important information about the prevalence of the virus in the community, as well as help scientists better understand immunity, health impacts, and transmission rates.

Many nations recognized early on that testing for the virus would be critical to any strategy to contain it. Although testing has ramped up considerably in the United States in recent months, multiple challenges remain. Testing availability, testing supplies, and test processing capacity in the United States are still not at all sufficient to meet growing demand. Many individuals experience long delays in receiving test results, effectively defeating efforts to undertake timely quarantining and contact tracing.<sup>1</sup> What’s more, not all tests products are of the same quality or accuracy, and more rigorous standards will need to be implemented to govern their use as additional evidence is generated.

To enable a better understanding of all of these issues for policy makers, this paper describes COVID-19 testing methods, the regulatory and reimbursement landscape around their development and use, and ongoing capacity, data, access, and payment challenges in carrying out more efficient testing. More specifically, this paper will answer the following questions:

- What Are the Types of Tests and How Do They Work?
- How Accurate Are Tests for the Novel Coronavirus and COVID-19?
- How Are COVID-19 Tests Regulated?
- How Much Testing Is the United States Doing Now and How Much Should Be Done?
- How are Testing Results Reported and Who Maintains the Data?
- How Much Do Tests Cost and Who is Paying for Them?
- What are the Biggest Challenges for Successful Implementation of COVID-19 Testing?
- What is the Way Forward?

## Applications of COVID-19 Tests

Developing a strategy for more efficient testing begins by matching the right test for the right purpose. Highly accurate **diagnostic tests** (often molecular laboratory tests, but also high-performing antigen tests) are used to test people with symptoms of COVID-19 or close contacts of people that have been diagnosed. Rapid return of results from these tests enable contact tracing and reduction in transmission.

In other scenarios, it is important to have a rapid method to screen individuals who are not suspected to be infected. **Screening tests** are used more frequently and have fast turnaround times (minutes to an hour), with the trade-off being that they are somewhat less accurate than definitive diagnostic tests. Screening tests should be used for people without symptoms or known exposure to someone with COVID-19, to give people more confidence about returning to workplaces and schools.

Additionally, there is a need for population-based **surveillance testing**, which involves research to inform and update community and regional policies but are not used to make decisions about whether individuals need to take actions like isolation.

## What Are the Types of Tests and How Do They Work?

### Test Types

COVID-19 tests are meant to determine whether a person is currently or has previously been infected with the SARS-CoV-2 virus, for the purposes of treatment, preventing spread of the disease, and understanding more about the virus (Table 1). There are three types of tests:

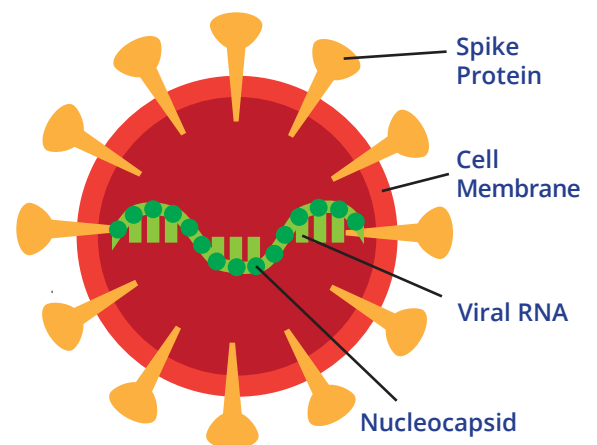
Molecular tests and antigen tests use samples from patients' respiratory tracts or saliva to detect the actual presence of the virus in the body (Figure 1). Molecular tests detect the virus's genetic material. Antigen tests detect specific components on the surface or within the virus. Both test types indicate whether a person has an active infection and should take steps to quarantine or isolate, so as not to spread the virus to others.

Samples for molecular and antigen tests are typically taken by inserting a swab into a person's nasal cavity or throat, although a few tests also sample a person's saliva. Nasal or throat swab tests normally need to be collected from individuals by healthcare workers or under their supervision. However, some manufacturers are developing tests that enable people to collect their own samples at home, like saliva-based tests that simply require people to spit into a tube, a process that does not require a healthcare worker to execute it. While potentially easier to conduct, regulators have concerns about consistency of sample collection using this method.

Serology, or antibody, tests are used to determine whether a person has been infected in the past. Although these tests can sometimes detect active viral infections, they are not recommended for this purpose because individual antibody

Figure 1:  
**Molecular and Antigen Tests  
Detect Unique Viral Components**

Molecular tests detect viral RNA. Antigens are viral components, like proteins or RNA, that are recognized by the immune system.



responses can be variable and usually are not present at very early stages of infection.<sup>2</sup> Instead, serology tests are deemed most useful for determining who previously had the virus and how much the virus has spread in a community. As part of the immune response to viral infection, a person's immune system develops antibodies that recognize and help eliminate the virus, and these antibodies circulate in the blood (or serum) (Figure 2). It is not yet clear whether having antibodies to the virus indicates that a person will be immune to the virus in the future. However, serology tests are useful to determine prevalence of the disease in a community, to screen for prospective convalescent plasma donors, and to increase understanding of how the virus spreads.

Samples for serology tests are frequently collected by taking blood from the patient through a needle and syringe, or less frequently by taking a smaller blood sample through a finger stick. As this point in time, blood samples for these tests are only collected by healthcare workers.

Figure 2:

## Antibodies are Produced in Response to Viral Infection

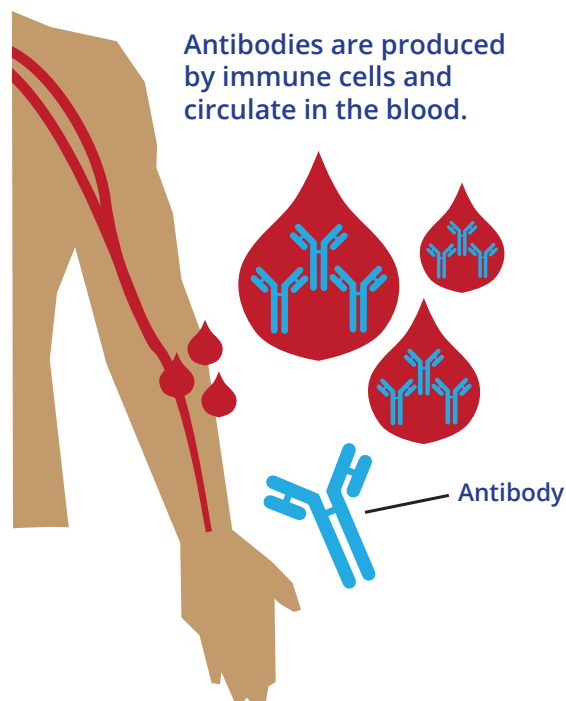


Table 1: Types of COVID-19 Tests

Test Type	Purpose	Component Detected	Sample Needed	Location of Testing	Analysis Time	Other Associated Terms	Considerations
Molecular	Identifies active infections used for diagnosis	Viral RNA	Nasopharyngeal, nasal or throat swab, saliva	POC or laboratory	Can be as fast as 30 to 60 minutes, but more accurate laboratory tests can take several hours	Diagnostic test, nucleic acid amplification test (NAAT), PCR test, LAMP, isothermal amplification	High sensitivity and specificity with lower probability of false negatives or false positives, but potential delays if sent to a laboratory for processing
Antigen	Identifies active infections used for diagnosis or screening	Viral proteins	Nasopharyngeal, saliva	POC	15 to 30 minutes	Rapid diagnostic	Rapid results, ideal for on site screening, but generally lower sensitivity means that some infections may be missed
Serology	Identifies past infections used for surveillance	Human antibodies	Blood	POC or laboratory	Can be as fast as 15 to 30 minutes, but more accurate laboratory tests can take several hours	Antibody test, blood test	Reliability of the result depends on prevalence and the protective effect of antibodies is still unknown

## *The Biology and Chemistry of Testing*

Viruses are complex assemblies of molecules – essentially nucleic acids (DNA or RNA) encased in a coat of proteins. They can do nothing until they enter a living cell, where they hijack the cell's own replication machinery to reproduce the virus's DNA or RNA and manufacture more viral protein. SARS-CoV-2 tests look for the proteins or the RNA that make up the virus, or for signs of the body's response to the virus in the form of antibodies. SARS-CoV-2 is in the family of coronaviruses, named for the crown-like protein spikes on the surface of these viruses. Many common cold viruses are coronaviruses, as are others that have proved more dangerous to humans, such as the Severe Acute Respiratory Syndrome (SARS) virus that caused a broad global epidemic in 2003, and the Middle Eastern Respiratory Syndrome (MERS) virus that was identified in 2012.

Testing is a complicated process that involves both the biology of the virus and the body's reaction to it, and the chemistry inherent in different methods of testing, as well as in the way that tests are processed. This section discusses these issues for molecular, antigen, and serology tests.

### **Molecular Tests**

Molecular diagnostic tests look for the presence of viral genetic material in samples taken from the body. Molecular tests are also referred to as nucleic acid amplification tests (NAATs), which can include the techniques of polymerase chain reaction (PCR) or isothermal amplification (Figure 3). Molecular tests detect the presence of some of the virus's genetic material – in this case, RNA – and can also quantify relative “viral load” – that is, the amount of a virus in a given person. Currently, there are more than 100 different types of molecular diagnostics that are available in the US for detecting the presence of SARS-CoV-2.<sup>3</sup>

### **Antigen Tests**

Antigen tests detect viral proteins and identify active viral infections, and they can be used for diagnosis or screening purposes. Antigens are substances that induce an immune response in the body; in the case of SARS-CoV-2, the spike or nucleocapsid proteins are frequently the target antigen. Antigen tests for SARS-CoV-2 employ a biochemical technique that detect fragments of viral proteins in samples collected from the nasal cavity using swabs (Figure 3). Although these tests are not useful in measuring viral load, they do work quickly to detect viral proteins, and currently available products are processed at the point-of-care (POC). To date, only two such tests, the Quidel's Sofia SARS Antigen test and the BD Veritor COVID-19 test, have been authorized for use under a US Food and Drug Administration (FDA) emergency use authorization (EUA).<sup>3</sup>

### **Serology Tests**

Serology tests can detect both active and past infections, but as noted above, are mainly used not to diagnose infections but rather to determine who has been infected previously. Serology tests are designed to detect whether a patient has experienced an immune response to the virus, signaled by the presence of antibodies (also called immunoglobulins). These proteins lock onto the SARS-CoV-2 virus, in effect tagging them so that other immune system cells can destroy the virus. Serology tests are run on blood samples from patients, and can be processed at either a laboratory or at POC (Figure 3).

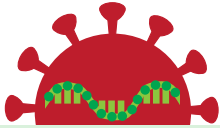
There are five antibody isotypes, of which IgM and IgG are frequently used to identify previous infections. The level of antibodies changes over time, with IgM antibodies appearing within days and then diminishing within several weeks, and IgG antibodies developing in later stages of infection and persisting months to years after infection. The serology tests developed for SARS-CoV-2 may test for IgM or IgG individually, both IgM and IgG, or total virus-specific antibodies (which does not specify between antibody isotypes). Although the presence of antibodies may suggest who has developed immunity to the virus, it is not known how long antibodies remain in the blood after infection, and therefore how long a patient may retain immunity that would protect against reinfection.<sup>4</sup>



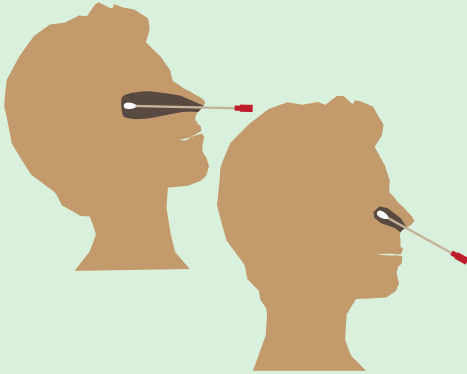
Figure 3: **How Various COVID-19 Tests Work**

### Molecular Test

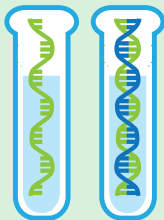
Detects viral RNA and positive results indicate active infection.



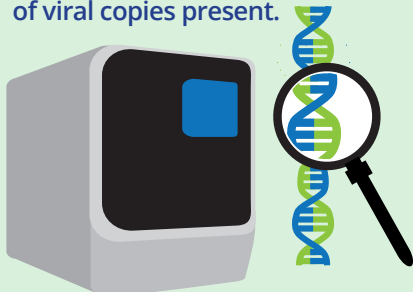
1. Obtain specimen using nasopharyngeal, nasal, throat, or saliva sample.



2. Extract RNA from sample and convert to DNA.



3. Using sample analyzer, amplify DNA and measure the number of viral copies present.



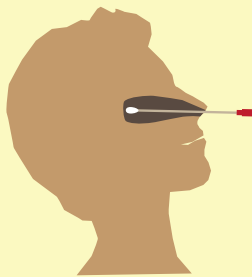
4. Rapid analyzers provide results of "Positive" or "Negative" within 30-60 minutes. PCR tests provide results in several hours.

### Antigen Test

Detects viral proteins and positive results indicate active infection.



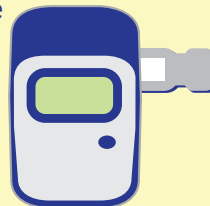
1. Obtain specimen using nasopharyngeal, nasal, or throat swab.



2. Break virus into pieces.



3. Sample is added to cartridge, which contains lab-made antibodies that detect viral proteins. Once processed, the cartridge is put in an analyzer.



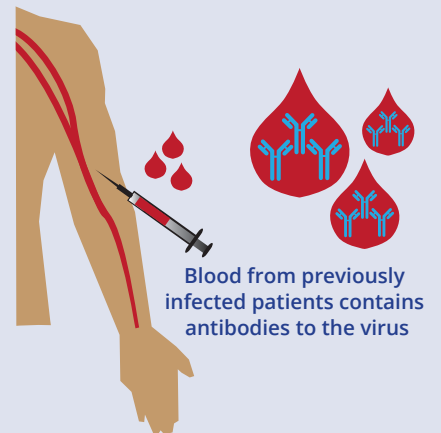
4. The analyzer "reads" the cartridge as either a positive or negative result. Antigen tests provide results within 15 minutes.

### Serology Test

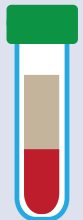
Detects antibodies to SARS-CoV-2 in blood; positive results indicate previous infection.



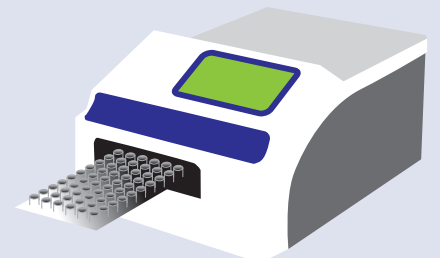
1. Obtain blood sample.



2. Blood serum, or fluid that contains antibodies, is separated from other blood cells.



3. Serum is added to test device – either a cartridge or a test plate.



4. Rapid, cartridge-based tests provide results within an hour. Laboratory-based tests provide results in several hours.

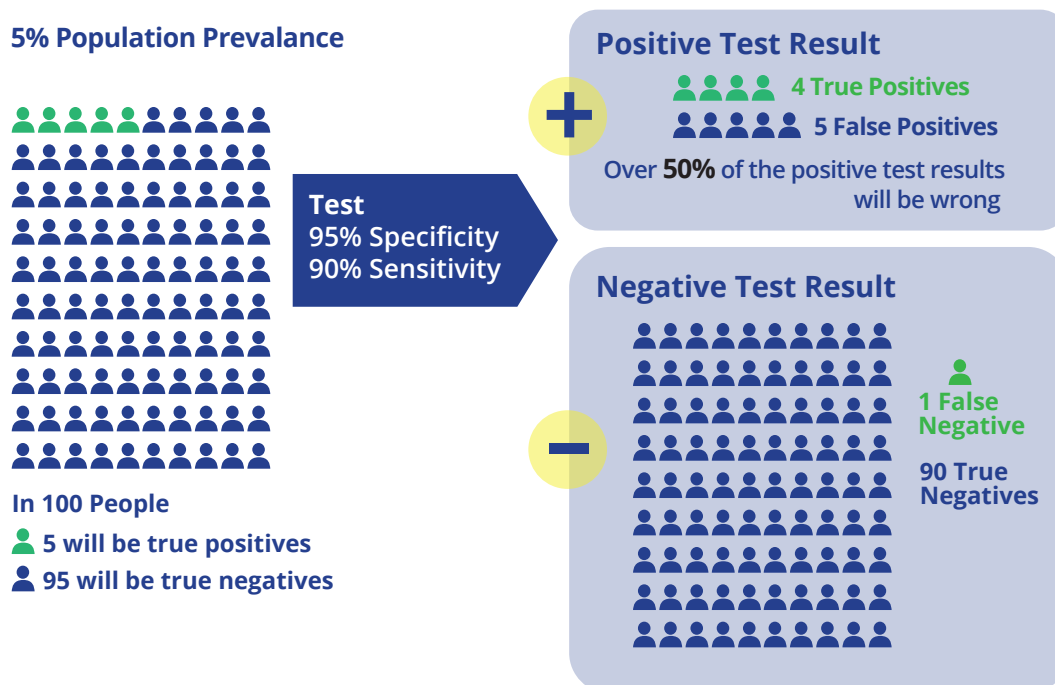
## How Accurate Are Tests for the Novel Coronavirus and COVID-19?

All medical diagnostic, screening, and surveillance tests, including tests for SARS-CoV-2 or COVID-19, have varying degrees of “sensitivity,” which is the likelihood that infected or sick individuals are correctly identified as such (true positives), and “specificity,” which means the likelihood that non-infected or healthy individuals are correctly identified as such (true negatives). These intrinsic characteristics can vary by type of test, so that some can be more sensitive or specific than others. In addition to producing false negatives, some tests will also yield false positives, which means that even some uninfected people will test positive for the virus.

Before they can be considered effective, tests must be validated to establish their performance characteristics as measured by sensitivity and specificity. These aspects of tests are expressed in terms of “positive predictive value” (PPV), which is the likelihood that a test correctly identifies people who do have an infection, and “negative predictive value” (NPV), or the likelihood that people who test negative truly do not have an infection. Sensitivity, specificity, PPV, and NPV are usually expressed in percentage terms along with a confidence interval, which essentially expresses the degree of confidence that the percentage results are correct. Because individuals, healthcare providers and systems, and public health authorities will make very consequential decisions on the basis of test results, it is very important that a test scores as high as possible in each of these domains.

Disease prevalence also impacts the reliability of test results. If only a low number of people in a community have been infected, then even a highly specific test can result in many false positives, simply because most people taking the test are not, or have not been, infected. For example, if there are no infections in the population, by definition any test that produced a positive result would be a false positive. On other hand, if everybody is infected, then any negative test result would be a false negative (Figure 4).

Figure 4: **How Disease Prevalence Affects the Predictive Value of a Test**



*In areas where very few people have contracted COVID-19, even fairly accurate tests can result in high proportions of false positive test results to true positive results. This figure shows how a test that just meets the FDA minimum rates of sensitivity and specificity used in a community which has had just 5% of its population contract COVID-19 will result in more than half of the positive tests results being false positives. (Note that the numbers listed in this figure are rounded to whole numbers.)*

The combination of all of these factors – sensitivity, specificity, PPV, NPV, and disease prevalence – thus determine how accurate testing is. The tests that are currently on the market have a range of values for sensitivity and specificity, though as is described in the next section, FDA requires a minimum of 90% sensitivity and 95% specificity for tests to be granted authorization for use.<sup>5</sup> Often, sensitivity and specificity values correlate with the amount of time that it takes to run a test: laboratory-based tests that take several hours to run are typically more accurate than POC tests that provide results in less than thirty minutes.

The level of accuracy will have different implications for test results, depending on the type of test that is used. For molecular or antigen tests, reducing the number of false negatives will be more important than reducing false positives. The consequence of a false negative is that an individual could unknowingly spread the virus to people that they come in contact with, perpetuating the outbreak. In contrast, a false positive may be burdensome for an individual, who will be asked to remain in isolation until their next negative test result, but there will be fewer negative consequences for society. In the case of a serology test, it will be particularly important for tests to have a high specificity (low chance of receiving a false positive result). People who test positive may be asked to take on tasks at work that have higher exposure risk and may engage in higher risk activities in their personal life, believing themselves to be immune. A false positive would increase both their personal risk of getting infected as well as potentially increasing the risk that they would infect others were they to become contagious.

## How Are COVID-19 Tests Regulated?

FDA is responsible by law for the regulation of COVID-19 medical devices, and thus regulates tests, which are considered devices. The agency has the authority to regulate both tests developed by commercial manufacturers for mass-market distribution and laboratory-developed tests developed by a single laboratory for its exclusive use. The agency also administers several regulatory pathways for the premarket clearance, approval, or authorization of COVID-19 diagnostics and has provided several regulatory tools, including emergency guidance, to help accelerate the availability of novel COVID-19 tests developed by laboratories and commercial manufacturers.

### *Regulating Commercially Manufactured and Laboratory Developed Tests For COVID-19*

Molecular, antigen, and serology tests are commercially manufactured “*in vitro*” diagnostic tests (IVDs) – meaning those tests performed in a test tube, dish, or elsewhere outside of the organism – they are considered medical devices, and thus are regulated by FDA’s Center for Devices and Radiological Health (CDRH) under the Federal Food, Drug, and Cosmetics (FD&C) Act. Commercial manufacturers must submit studies confirming a test’s accuracy and usefulness in diagnosing a particular condition to CDRH before bringing it to market, and CDRH verifies these test features.

Commercially-manufactured medical devices are classified as being in one of three different “risk” categories, ranging from low to moderate to high risk, based on the degree of regulatory control that is deemed necessary to ensure that devices are safe and effective. Accordingly, the FDA has several different regulatory pathways for clearing or approving these devices based on risk. Medical tests are considered “high risk” if the potential harm to a subject from an inaccurate test result could be life-threatening, or present a serious risk to the subject’s health, safety, and welfare. These high risk tests are subject to premarket approval by FDA before they can be allowed onto the market. Devices or tests considered to be low to moderate risk proceed along different regulatory pathways. One of these pathways, known as “510(k)” covers devices that are equivalent to devices already on the market. For these devices, premarket clearance (a lower regulatory bar) rather than approval is needed. The other pathway is “*de novo*.” This pathway is used to clear low and medium risk devices that do not have a comparable device on the market, so FDA cannot use existing equivalence criteria as the basis for granting premarket approval.

Laboratory developed tests (LDTs) are types of in vitro tests that are designed, produced, and used within a single laboratory, such as that of a hospital or an academic medical center. They are distinct from tests that are developed by a commercial manufacturer and then sold and used broadly across multiple labs and settings. LDTs are often created for a specific purpose or in response to unmet clinical needs, such as a genetic test for a small population of people with a rare disease. LDTs function similarly to many FDA-cleared or authorized tests. Under FDA's legal authority of enforcement discretion, the agency has historically not enforced premarket review requirements for LDTs because of their narrow focus and limited availability.<sup>6</sup> Instead, FDA has delegated regulation to the Centers for Medicare and Medicaid Services (CMS), which ensures that laboratories meet federal standards under a body of law known as the Clinical Laboratory Improvement Amendments (CLIA) to the Public Health Services Act.

From the start of the COVID-19 pandemic in March through mid-August, however, FDA asked LDT developers to submit test performance data to the agency for review, and then issued EUAs once it was satisfied about LDT tests' performance and accuracy. The agency also allowed certain LDTs to be run in high-complexity CLIA laboratories as soon as those tests were validated and the FDA was notified, before the issuance of a formal EUA.

On August 19, 2020, HHS issued a "Rescission of Guidances and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests." This document eliminated FDA's premarket review of LDTs unless performed through notice-and-comment rulemaking, a potentially lengthy process under which FDA would signal its intent to regulate LDTs, solicits stakeholder comments, considers those comments, and then issues a final regulation. The HHS statement further noted that the department's action was intended to keep "duplicative regulations and unnecessary policies" from interfering with efforts to introduce COVID-19 tests.<sup>7</sup>

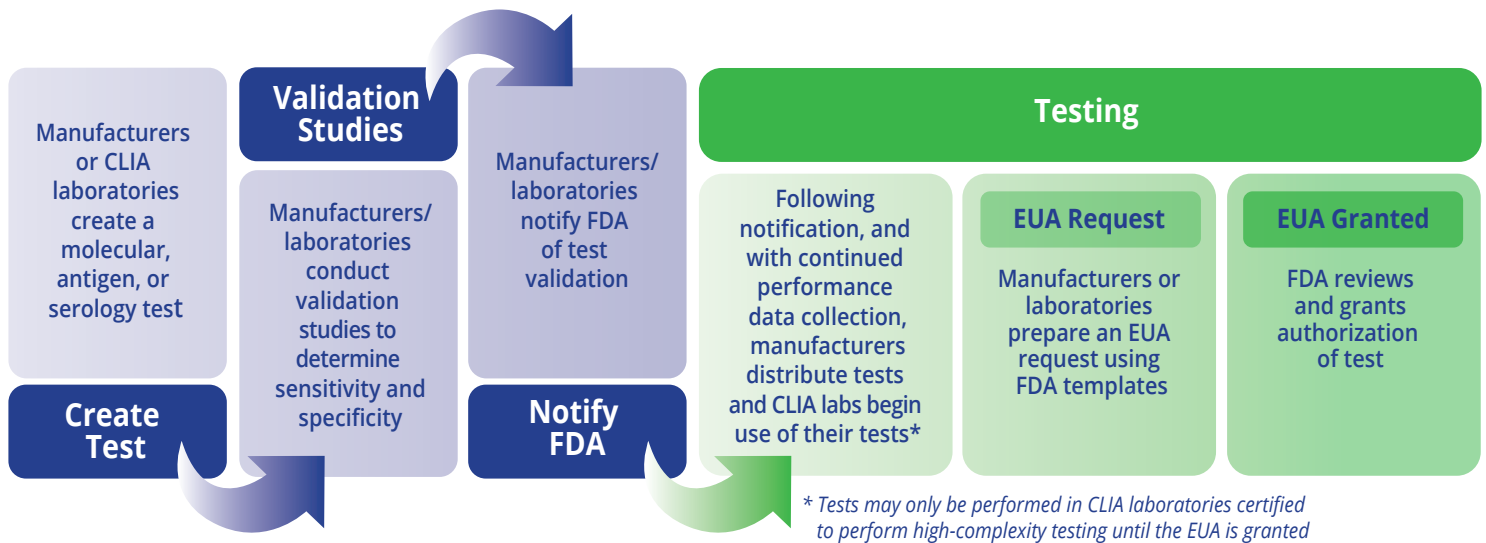
As a result of the HHS announcement, LDTs can now be administered by the laboratories that have developed them without authorization from the FDA – although LDT developers may still submit performance data to FDA, and request an EUA if they wish. Laboratories producing LDTs continue to be regulated under CLIA, which means that they are subject to quality standards governing such areas as test accuracy; states also have authority to regulate CLIA laboratories. These changes may result in an increase in test capacity as more laboratories begin to develop and administer their own tests, without experiencing any delay from waiting for an EUA from FDA. However, the trade-off could further uncertainty and ambiguity around test performance, specificity, and sensitivity, and therefore lead to less confidence in these tests from purchasers, providers, and patients.

### *Emergency Use Authorizations*

Typically, it can take months or even years for IVDs to receive approval or clearance from FDA. However, in late January 2020, in response to the appearance of the SARS-CoV-2 virus, the Secretary of the Department of Health and Human Services (HHS) declared a National Emergency under the Public Health Service Act and authorized emergency use of IVDs that detect or diagnosis the virus.<sup>8</sup> Because the FD&C Act gives the FDA commissioner the ability to allow unapproved medical products to be used in an emergency, the FDA followed with its own emergency guidance for test developers. The agency has also made it explicit that an IVD made available under an EUA has not undergone the same type of review as an FDA-approved or cleared IVD.

Since March 2020, the agency has issued EUAs for both commercially-manufactured and laboratory-developed molecular, antigen, and serological tests, as well as for modifications of existing tests. CDRH has refined and modified its process for granting EUAs over the course of the public health emergency and has created templates to help manufacturers understand what information is required for FDA to efficiently review their EUA application, as well as information on test validation and minimum performance attributes (Figure 5). FDA has updated these templates throughout the public health emergency. In July 2020, for example, it issued EUAs allowing two private laboratory testing companies, Quest Diagnostics and LabCorp, to start pooling up to five individual swab specimens and testing them as if they were one sample.<sup>9,10</sup>

Figure 5: **Steps for the Preparation and Submission of an EUA**



For a period of time between March and May 2020, CDRH also provided flexibility for serology tests to be marketed with notification to FDA and certain labeling information, but without submission of an EUA. It offered this flexibility because such tests are not designed to diagnose infection, but rather to show infection prevalence in different communities, among other uses. In April, the Agency issued an umbrella EUA for commercial serology tests evaluated by the National Institutes of Health's National Cancer Institute, through a multi-agency effort to create an independent "testing ground" to validate serology tests. However, it has since terminated the umbrella EUA in favor of authorizing the use of serology tests on an individual EUA basis.<sup>11</sup> FDA has authorized several serology tests under individual EUAs and makes a list of EUA authorized serology tests available on its website.

CDRH publicly posts performance information about molecular, antigen, and serological tests that have received an EUA. It also posts the names of tests that are in the process of being reviewed but may be marketed throughout a pre-authorization period during which the manufacturer or laboratory is preparing materials to request an EUA after test validation. While FDA has granted permission for pre-authorization use of molecular, antigen, and serology tests to CLIA laboratories certified to perform high-complexity tests, the extent to which the tests are used during this pre-EUA period is not well understood because some buyers are apprehensive to purchase tests that have not yet been authorized by the FDA. Tests may also be removed from the market if the real-world performance or subsequent validation testing shows problems with the test's performance.

Because the public health emergency has now been extended to the end of October 2020, these EUAs are likely to remain in effect for at least that long. In fact, EUAs issued during the Zika and Ebola public health emergencies have endured for several years after the initial emergency declarations, including 10 EUAs issued for Ebola diagnostics between 2014 and 2019.<sup>12</sup> However, FDA policy indicates that EUAs issued under the public health emergency will end with the termination of the public health emergency.<sup>13</sup> Upon the termination of an EUA, public health and hospital-based laboratories are instructed to discontinue use of EUA-authorized tests for COVID-19. To continue marketing tests previously authorized under an EUA, commercial diagnostic manufacturers will need to submit for FDA clearance or approval.<sup>13</sup>



## How Much Testing Is the United States Doing Now and How Much Should Be Done?

### *Limitations to Testing Capacity*

As the time of publication, more than 5.5 million samples per week are being tested in the United States. However, expanding outbreaks around the country suggest that this number is far too low. Many stakeholders have called for maximizing the number of tests that are run to ensure that infected individuals are isolated before exposing others, and to determine whether we as a society are making progress against the virus. Yet the quantity of tests run is limited by the capacity within laboratories, the available supply chain, and guidelines for who gets priority testing.

At this time, the majority of available tests must be processed in a clinical or reference laboratory, with the rest processed at POC, such as a doctor's office or pharmacy. Processing tests can be done on the same day as the test is taken in some locations, but it can also take up to a week or more if the test is processed in an offsite laboratory or if there is a backlog of tests. New POC approaches are emerging; for example, in June 2020, FDA issued an EUA for a POC molecular test and platform produced by Cue Health, which collects a nasal swab from a patient, detects SARS-CoV-2 viral RNA, and delivers test results to a mobile device in less than 25 minutes.<sup>14</sup> In the future, it may be possible for both sample collection and sample processing to take place in an individual's home or outside of a clinic.






For non-POC tests, there are a number of steps that must occur between sample collection and dissemination of a result. It is these intermediate steps that can cause delays in processing and that are often affected by disruption of the supply chain.

If a laboratory wants to bring in new equipment for testing, the laboratory must purchase the equipment, have it installed, and train its staff on its use. Under normal circumstances, this process can take months, and there might be limits in staff time or manufacturer's setup that would prevent significant acceleration of this process. Once the equipment has been installed, or if a laboratory already has the equipment in place, the laboratory must validate the test in its facility and notify the FDA of its use.

Another issue that has been contributing to the recent delay in test results is that there is a lack of interoperability between different manufacturers' test equipment and kits. That is, equipment from manufacturer A will only work with a test kit from manufacturer A, and not from manufacturer B. In other cases, kits use proprietary reagents that are specific to whichever manufacturer has created the test, so generic manufacturers cannot recreate the components. This incompatibility, paired with shortages in kit supplies, means that laboratories sometimes have unused capacity while also dealing with a backlog of samples.<sup>15</sup>

In addition to the equipment associated with the actual test, for each test, the processes of collection, transport and analysis require ancillary components (Figure 6). These components may include personal protective equipment (PPE) for test administrators, collection swabs, needles, sterile tubes, transport media, nucleic acid processing kits, test control kits, and other various reagents. With the rapid increase in demand for these products, there have been rolling shortages associated with these supplies. While the capacity of U.S. laboratory supply chains has improved, many laboratories still face uncertainty about their ability to procure needed supplies on a long-term basis.

Figure 6: **Testing Lifecycle**

	 <b>Collect Sample</b>	 <b>Transport Sample</b>	 <b>Prepare Sample</b>	 <b>Run Analysis</b>	 <b>Report Results</b>
<b>What is Needed</b>	<ul style="list-style-type: none"> <li>• Swabs</li> <li>• Collection vials</li> <li>• Personal protective equipment (PPE)</li> <li>• Trained healthcare staff</li> </ul>	<ul style="list-style-type: none"> <li>• Transfer media</li> <li>• Proper tagging and routing of samples</li> <li>• Climate controlled storage</li> </ul>	<ul style="list-style-type: none"> <li>• Test reagents or test kits (different tests require different supplies)</li> <li>• Materials to extract RNA and convert to DNA</li> <li>• Laboratory materials (e.g. culture plates, pipette tips, plastic tubes)</li> <li>• PPE</li> <li>• Trained laboratory personnel</li> </ul>	<ul style="list-style-type: none"> <li>• Machines to run samples</li> <li>• PPE</li> <li>• Trained laboratory personnel to interpret test results</li> </ul>	<ul style="list-style-type: none"> <li>• Transferring results from laboratory data systems to EHRs</li> <li>• Systems and protocols for reporting results to individuals</li> <li>• Interoperable data systems</li> </ul>
<b>What Can Cause Delays</b>	<ul style="list-style-type: none"> <li>• Shortages of personnel</li> <li>• Limited opportunities for at-home collection</li> <li>• Shortages in any of the above supplies</li> </ul>	<ul style="list-style-type: none"> <li>• Time of collection</li> <li>• Location of test collection site</li> </ul>	<ul style="list-style-type: none"> <li>• Shortages of personnel</li> <li>• Shortages in any of the above supplies</li> </ul>	<ul style="list-style-type: none"> <li>• Limited number of machines and capacity of each</li> <li>• Shortages of personnel</li> <li>• Shortages in any of the above supplies</li> </ul>	<ul style="list-style-type: none"> <li>• Insufficient interoperability</li> <li>• Inadequate electronic reporting systems</li> </ul>

### *Guidelines for Test Deployment*

At the beginning of the pandemic, tests were limited to individuals who were showing symptoms and had been in contact with someone who had tested positive or had been to a region where there was an outbreak. Since that time, scientific studies have shown that a large portion of those who are infected are asymptomatic, and that they can spread the virus despite the lack of symptoms. In June, the Centers for Disease Control and Prevention (CDC) released a consolidated list of factors to consider when deciding who should be tested.<sup>16</sup>

In part because CDC guidelines are recommendations, not mandates, individual states have developed their own guidelines for testing people and have rolled out varying levels of testing capacity. As a result, the number of tests being run in a week increased nearly five-fold between March and July 2020.<sup>17</sup> However, whereas the bottleneck at the beginning of this crisis was not having enough tests for those who needed them, testing is now slowed by not having the capacity to process test samples quickly enough. There are reports that it can take up to 10 days to get results of a test.<sup>18</sup> Very unfortunately, that is sufficient time for the virus to spread extensively if the tested individual does not remain quarantined while awaiting the test result.

To help identify individuals who need to be tested, contact tracing is recommended. Contact tracing involves identifying and following up with individuals who have been in contact with other people who have tested positive for SARS-CoV-2. Contact tracing can also help generate data about how the virus is spreading, as well as improve understanding of how the virus is transmitted. However, there have been multiple challenges in standing up contact tracing networks, since the resources available to support these efforts vary greatly by locality, state, and region. Contact tracers are also encountering challenges in getting critical information from infected individuals; many people have been refusing to share details of where they had traveled or who they had contact with immediately prior to testing positive.

In the absence of any more robust or directive federal testing strategy, states and localities will continue to have lead responsibility for adoption and implementation of testing strategies. The National Governors Association has assembled a comprehensive list of steps that states have taken to date, including establishing criteria for who should be tested and according to what priority; creating a testing advisory group; establishing community-based testing sites, including drive-through and mobile sites; use of serology tests as part of a state surveillance effort; issuing standard orders for testing or not requiring provider orders; expanding Medicaid coverage for testing; and reporting testing on public dash boards or other venues.<sup>19</sup> In addition, a group of states have set up purchasing contracts with manufacturers to ensure that they have the needed supply of tests.<sup>20</sup> Since no state appears to have engaged in all of these activities, state and local policy makers must be attentive to whether enough planning, coordination, and implementation is under way.

In the future, it is likely that novel lower cost and rapid turnaround screening tests will be used to determine whether individuals are healthy enough to attend work or school.<sup>21</sup> States and local governments will need to develop frameworks to guide screening frequency, as well as prioritization guidelines to ensure that those who most need to be tested obtain it in a timely manner. This challenge is discussed further below.

### *Determining the “Best Tests”*

As the number of test manufacturers with EUAs increase, people and organizations seeking tests are likely to want to use the “best” tests. Defining “best” requires consideration of a number of factors, including price, time to results, and accuracy of tests. Provider preferences and familiarity with certain tests may also drive demand.

Having complete and accurate information will be important to test users, and many may benefit from centralizing that information for easy access. For most tests, there is a trade-off between sensitivity and specificity, in much the same way that airport passenger screening technology may trigger alarms on low-risk items like passengers’ belt buckles (low specificity) to increase the probability of identifying truly dangerous objects (high sensitivity). For each set of users, it will be important to understand what characteristic of a given test is most important, and for what purposes. For screening purposes, a highly sensitive test that almost never misses a true positive could be most valuable to detect infections and promptly isolate potentially infectious individuals. For diagnostic purposes however, a highly specific test that rarely registers positive for anything other than SARS-CoV-2 ensures that patients get appropriate treatment.

Many times, there will be a trade-off in sensitivity or specificity and time to results. In these cases, it will make the most sense to evaluate the situation in which the test is used and the prevalence of infection in the local environment. For example, the currently available antigen tests produce rapid results, but may miss some positive cases – or in recent cases like Vermont and Connecticut – identify a large number of false positives.<sup>22,23</sup> If the tests are being performed in a high prevalence area and are being used to determine if an individual can come to work that day, a certain number of false positives might be an acceptable trade-off for real-time information and preventing continued spread. Confirming results with more accurate PCR testing could then allow people that received initial false positives to return to work or school more quickly.

Dissemination of information on test quality and accuracy may depend in part on requirements set by the FDA. Ultimately, stakeholders will want to prioritize tests to enable a shift in capacity for those that provide the most value for providers, patients, and public health systems.

## How are Testing Results Reported and Who Maintains the Data?

Commercial, reference, public health, and hospital laboratories report testing data for certain infectious diseases to public health authorities, with exact reporting rules defined by states of residence. In turn, public health authorities feed the data to the CDC's National Notifiable Diseases Surveillance System (NNDSS).<sup>24</sup>

Throughout early 2020, states issued orders or guidance on laboratory reporting of SARS-CoV-2 testing, and began reporting these data on their public health websites.<sup>25</sup> With a need to provide a nationwide picture of diagnostic testing, several efforts sprang up to collate state data, such as the volunteer-run COVID Tracking Project or the a similar effort by the New York Times, with different levels of aggregation and inputs (only the COVID Tracking Project collects negative tests).<sup>26,27</sup>

State provided data did not have universal standards, resulting in a lack of consistency across the compiled cross-state data. Initially, some states only reported positive results and not the total number of tests that were run. For a time in May, with the reopening debate raging, some states began reporting significant increases in the number of tests performed, only to later disclose that they were inappropriately counting serology tests in total test counts.<sup>28,29</sup> In addition, many states shifted from reporting the number of people tested to reporting on the number of specimens tested, which provided higher total test counts. Demographic information, like age and race, was often missing from this reporting, and few states identified spread in congregate settings like nursing homes and prisons, making it difficult to assess the uneven burden of this epidemic.

Progress has been made on improving quality and consistency of test data reporting on the state level. To encourage more systematic reporting, the COVID Tracking Project began to issue data quality grades to states, reflecting testing data completeness, availability of demographic data, and reporting practices.<sup>30</sup> The federal government, through HHS, also issued guidance on the types of laboratory data that needed to be reported as a part of the Coronavirus Aid, Relief, and Economic Security (CARES) Act.<sup>31</sup> This guidance applies all laboratories offering SARS-CoV-2 tests. This requirement includes information on tests used, test results, and individuals being tested. Laboratories are required to submit this data directly to state or local public health departments, who will then submit de-identified data to the CDC on a daily basis. Laboratories were required to report these data components no later than August 1, 2020.

However, many critical data are still not being reported consistently. Of the five testing indicators that epidemic experts at Resolve To Save Lives identified as essential, such as time until results or total testing in congregate settings, not one was reported by all states as of late July 2020.<sup>32</sup> Notably, not a single state reports test turnaround time, which contributes to successful strategies for rapid isolation of positive cases.

The introduction of antigen testing is also contributing to reporting inconsistency. There are concerns that positive antigen tests are not being reported to states, increasing the difficulty in assessing the state of the status of outbreaks. While these tests may be less sensitive than laboratory-based molecular tests, backlogs in laboratory testing are on the rise and test administrators are increasingly using antigen tests to make a diagnosis. Capturing these data will be critical.

Further, inconsistent data standards remain a concern. Lack of standards for reporting race or age groups makes creating a national picture of the epidemic's burden very challenging. There are also significant discrepancies between the state and CDC reporting of total tests conducted.<sup>33</sup> The data that CDC began reporting on May 8, 2020 appear to be drawn from data reported by states, with an attempt to remove state-reported serology tests.<sup>29</sup> However, these adjustments do not explain why some states report fewer tests than what is subsequently reported by CDC.

## How Much Do Tests Cost and Who is Paying for Them?

### *The “Costs” of COVID-19 Tests*

There are a number of perspectives inherent in any discussion of the “costs” of COVID-19 testing. At one level, there is the actual cost of producing different types of tests. At the next level are prices: What are manufacturers or laboratories charging for these tests? There is also the question of reimbursement: How much are payers actually paying for these tests, and how is that burden being shared among payers and individuals receiving the tests? And finally, there is the question of the level of overall expenditures: What are total outlays for paying for these tests, at a local, state, or national level?

Costs of producing tests will vary by line of business and testing strategy. For many molecular tests, the machines running the samples constitute the greatest expenditure. Once the machine has been purchased, many laboratories suggest that the PCR and serology testing techniques are relatively simple, and by extension, low cost. Antigen testing is estimated to cost less than five dollars.<sup>34–36</sup> Growing demand for testing might drive more resources into developing testing infrastructure and technologies and lower absolute costs of tests.

With regard to prices or charges, several commercial laboratories have posted test price information ranging from \$59 to \$229 per test.<sup>37</sup> The American Clinical Laboratory Association, whose members have completed over 11 million tests, states that most members charge between \$95 to \$209 per test.<sup>38</sup> One analysis of 29,160 coronavirus test bills found that 87% of tests have been billed at \$100 or less.<sup>38</sup> Providers and laboratories purchase molecular or antigen tests directly from manufacturers at the manufacturer’s set price, and sometimes may bill insurance companies for the test at a higher price. There have been examples of billing at higher rates, up to \$6,000 per test, leading to a Congressional investigation.<sup>39</sup>

The next cost consideration is reimbursement, which may vary by payer. CMS has set testing reimbursement rates between \$50–\$100 per molecular test and between \$40–\$60 per serology test.<sup>40,41</sup> CMS created a code for antigen testing, but Medicare Administrative Contractors have yet to set a reimbursement rate.<sup>42</sup>

Because no patient cost-sharing is allowed during the public health emergency, Medicare reimbursement figures become the de facto prices for tests; if providers or laboratories paid more or spent more to provide the tests, they must absorb the difference for Medicare beneficiaries. Private payers’ reimbursement rates, meanwhile, are not as transparent but are likely tracking closely with Medicare reimbursement as they’ve adopted the same coding practices. Current analyses suggest that tests in the commercial setting will be reimbursed at about 25% more than in the Medicare and Medicaid settings.<sup>43</sup>

Regardless of test used, providing an adequate amount of testing in the US will create significant expenses. A recent AHRP-funded analysis suggests that costs of diagnostic testing for COVID-19 at current testing levels may total between \$6.0 to \$25.1 billion annually depending on tests utilized, and commercial insurers are expected to shoulder \$2.3 to \$13.3 billion of that spending.<sup>43</sup> As the federal government and states focus on further ramping up testing capacity, even more funds will be required.<sup>44</sup> One frequently cited roadmap to reopening recommends the allocation of \$100 billion to states for ubiquitous testing.<sup>45</sup> Current funding may fall short as the Families First Coronavirus Response Act appropriates \$1 billion to reimburse providers for COVID-19 testing for the uninsured.<sup>46</sup>



## *Testing Coverage and Access*

COVID-19 diagnostic testing is widely covered through several non-traditional routes that have been activated or put in place in response to the pandemic. CMS coverage decisions, typically made within the formal National Coverage Decision process, have instead been established outside of this process for timeliness and uniformity.

Since February, guidance and coverage for testing has evolved with the regulatory and development landscape.<sup>47</sup> The Families First Coronavirus Response Act initially required insurance coverage for FDA authorized tests; at the time that the law was enacted, there were roughly 10 authorized tests.<sup>48</sup> In mid-March, the FDA updated its guidance to allow clinical laboratories to create and perform COVID-19 tests without an EUA.<sup>49</sup> Despite payer concerns over covering unauthorized tests, the Act was subsequently strengthened to require coverage not only of EUA-authorized tests, but also of other COVID-19 tests awaiting an EUA from the FDA. Coverage is also now mandatory for all tests that have been developed in or authorized by a state that has notified HHS about such tests, as well as of any other tests determined to be appropriate under HHS guidance.<sup>50,51</sup>

Medicare coverage and reimbursement levels often influence the policies of other payers, and as a result, CMS's updated rules set the standard for much of the nation's coverage, whether private or public. Three key Medicare coverage decisions announced on April 30th, in effect for the duration of the public health emergency, have been particularly impactful:<sup>50</sup>

1. Medicare no longer requires proof of a written practitioner's order to cover testing for beneficiaries, a change that has encouraged the creation of pop-up and community testing sites where individuals can come for testing without a prescription or other doctor's order.
2. Medicare and Medicaid will cover certain serology tests.
3. Medicare and Medicaid will cover the processing of certain FDA-authorized at-home tests, where samples are collected by the patient and sent to a laboratory.

Many of the commercial health plans have followed suit, covering FDA-authorized tests, including those approved for patient use through pre-market approval and emergency use pathways, for members enrolled in Medicare Advantage, Medicaid, and Individual and Group Health Plans.<sup>51</sup> Medicare and commercial plans require tests to be ordered by a physician or healthcare professional, but unlike most commercial plans, Medicare does not require documentation of the order to receive testing.<sup>52-54</sup>

## *Ban on Patient Cost-Sharing*

Recent legislation, including the CARES Act, has required health plans to cover testing services when medically appropriate without any cost-sharing by patients or consumers.<sup>55</sup> For these plans, a test is considered medically appropriate if it has been ordered by an attending physician or other qualified health professional, following accepted standards of practice. This requirement went into effect on March 18th, 2020 and will extend at least through the duration of the public health emergency. The mandate applies to both IVD and serologic tests authorized by FDA to detect SARS-CoV-2 or diagnose COVID-19. It also includes other COVID-19 tests awaiting an EUA from the FDA, those that have been developed in or authorized by a state that has notified HHS, or tests determined to be appropriate under HHS guidance.<sup>51</sup> Some commercial plans have extended the ban on cost-sharing to last through the remainder of 2020, while many are in place indefinitely, at least through the duration of the public health emergency.<sup>52,54</sup>

Evolving guidelines, and adherence to the guidelines, has led to occasional billing problems in which patients are charged for testing services. While many health departments and insurers have tried to clarify that if a doctor orders a patient's test, the patient will not have to pay, some experts point out that individuals may still be fearful of being charged for testing, and that this factor may contribute to an underutilization of testing resources.<sup>56,57</sup>

## Coding

Normally, after Medicare or any other payer determines that it will cover a medical product or service, a new identifying code must be created so that the provision of the product or service can be reported, and so that it can be billed for, and reimbursed. There are two main types of codes: Common Procedure Terminology (CPT) codes, which were developed by the American Medical Association and which apply to different medical, surgical, and diagnostic services, and Healthcare Common Procedure Coding System (HCPCS) codes, which embrace the CPT codes and also apply to non-physician products, supplies, and procedures.

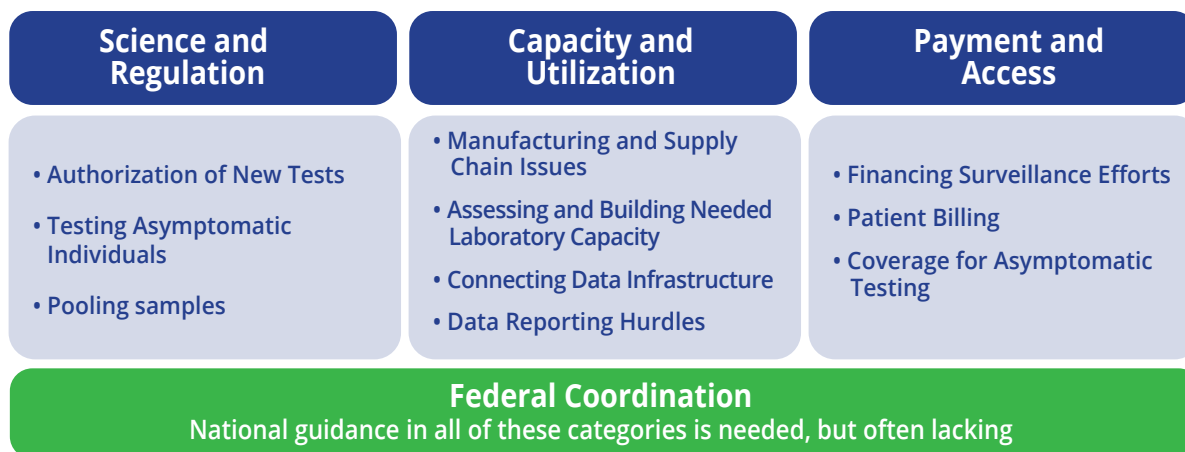
At the outset of the pandemic, there were no specific codes for COVID-19 testing, although that problem has since been largely rectified. In addition to facilitating payment for COVID-19 testing, accurate and specific coding may be a useful tool in tracking outbreaks and the magnitude of testing. Prior to the adoption of standardized, COVID-19-specific codes, tests were claimed under miscellaneous codes, which did not support data collection and tracking. According to many experts, it may now be necessary to develop additional codes for testing to assist in public health surveillance, and to provide data that can underpin national reopening or testing strategies.

The first COVID-19 test code was for the CDC-developed real-time PCR diagnostic panel and was adopted by CMS on February 13th, 2020.<sup>58</sup> Since then, more testing codes have been created by CMS and other bodies, and many commercial health plans have adopted most, if not all, of these codes. At present, codes for COVID-19 diagnostic tests specify the technique, type of specimen, type of detection (e.g. virus, antibody, antigen), and laboratory (whether a CDC-affiliated laboratory or a non-CDC affiliated laboratory).<sup>59</sup>

One major outstanding coding issue remains: to date, no new codes have been created for serology tests. Instead, pre-existing CPT codes that are not specific to COVID-19 tests are being used for these tests. The result has been confusion over coding that has occasionally led to improper denials of payment for the tests, as well as to payment rates that are decidedly lower than Medicare's set rate of approximately \$43 for serologic tests.<sup>40,57</sup> As indicated above, the creation of new codes for antibody testing may be helpful in tracking outbreaks and assessing the prevalence of previous SARS-CoV-2 infection.

## What are the Biggest Challenges for Successful Implementation of Novel Coronavirus Testing?

Figure 7: Challenges Associated with COVID-19 Testing



## Science and Regulation

Due to the novelty of SARS-CoV-2, there are a number of unanswered scientific and clinical questions that scientists, clinicians, and regulators are trying to answer while creating products and managing care of patients (Figure 7). A strong scientific understanding of how the virus behaves during infection, and how the immune system responds to viral infection, is needed to optimize tests and testing protocols. Since regulators are tasked with evaluating the safety and efficacy of new products, these outstanding questions have created some difficulty in evaluation of tests for the contexts that they might be used in. Key challenges for the coming months are described below.

### Authorization of New Tests

As the scope of the pandemic worsened in March 2020 and beyond, many manufacturers developed and imported tests for COVID-19, thus generating an enormous influx of applications for test approval to FDA. Some of these manufacturers are established diagnostic companies, but others have less familiarity with FDA requirements and regulations. In addition, FDA has required that individual laboratories receive an EUA for their LDTs, whereas in the past, these tests have not been regulated. The combination of manufacturer and laboratory applications quickly exceeded the CDRH virology team's capacity to review, with one estimate that applications increased 60-fold.<sup>60</sup>

FDA quickly worked to more than double the review staff, and also tried to streamline reviews by issuing guidance documents, publishing EUA templates detailing validation methods and components, making validation reference panels available to manufacturers, holding weekly town hall calls, and creating a frequently updated Q&A page, among other supports. FDA has also prioritized test reviews based on public health importance, which has meant that POC tests, tests that can be run in batches of more than 200 (called "high throughput"), and collection kits for tests that can be performed without a health professional's supervision have been subjected to faster reviews. However, for tests that have submitted an application to FDA for an EUA, there continues to be significant lag time to have that application reviewed and approved.

These delays are particularly an issue for serology tests because they are considered lower priority. As described above, once a serology test has been put on the EUA notification list, and the manufacturer submits its application to the FDA in a timely manner, an EUA approval is not required for the manufacturer to sell its test. However, potential customers for these tests have been hesitant to purchase those that have not formally received an EUA, impacting the availability and profitability of the serology tests awaiting official FDA authorization. These issues surrounding delays in EUA issuance have the potential to dissuade manufacturers from making further investments in serology testing capacity and production. A better understanding of the role of antibodies and what they mean for subsequent infections might also help manufacturers make a case for these tests being higher priority.

In addition, truly novel tests benefit less from guidance documents and templates based on the most common methodologies, and often require input from FDA on the precise forms of test validation that will be required to determine whether a test should be used. The significant review burden on the CDRH staff means that these discussions are also delayed. Both the agency and manufacturers believe that more support for FDA review will be critical to getting safe and effective tests to market faster.

## Ensuring Accuracy of Laboratory-Developed Tests

The policy announcement from HHS that eliminated regulation of LDTs by FDA will create new opportunities to increase testing capacity, as individual laboratories create and administer new tests. There are also opportunities to develop new state-based frameworks around testing validation, as well as new state-based infrastructure to track and validate test outcomes (although the ability of some states to conduct these activities amid the pandemic remains uncertain). However, amid a possible proliferation of tests, there may be even greater uncertainty about test accuracy, and therefore heightened potential for individuals to receive incorrect test results. It will be important for policymakers at the federal and state levels to monitor the situation throughout the public health emergency to ensure that the tradeoff of more tests, and fewer layers of regulation, does not have the unintended consequence of producing far more inaccurate test results.

## Testing Asymptomatic Individuals

As testing capacity increases, there may be a benefit to screening individuals who do not show symptoms of COVID-19, nor have reason to believe they are infected. Screening will be useful because some scientific evidence suggests that people may be most infectious before they develop symptoms and 40% of infected individuals never develop symptoms.<sup>61</sup> Screening tests can be used to detect outbreaks sooner and give people more confidence about returning to workplaces and schools – especially in high-risk settings like nursing homes, essential workplaces, and hard-hit communities that have limited resources to support testing. However, while LabCorp received authorization to test asymptomatic individuals, under current regulations, most molecular diagnostic tests are not authorized for use on asymptomatic individuals, for reasons discussed below.<sup>10</sup> All the same, many questions remain about when and how to test these individuals, and they pose a large quandary for regulators and the public health community.

A central question is whether the accuracy of tests is similar when they are performed on symptomatic and asymptomatic individuals. Although evidence is emerging that asymptomatic individuals have or shed similar levels of virus as symptomatic individuals, there is still much to learn including whether similar immune responses, such as antibody production, will develop when people experience no symptoms. If virus or antibody levels are lower than in those who are not outwardly symptomatic, then the detection limit of any given test – the lowest quantity or concentration of the virus or any of its components that a test can detect – will have to be lower as well. However, lower limits of detection can also affect a test's sensitivity, potentially leading to an increase in false positives.

Developing protocols for asymptomatic screening has been difficult because there is no existing reference standard to rule out whether the result is a false negative or a false positive. As a result, some experts have deemed reference standards for measuring test sensitivity in asymptomatic people an urgent priority, and FDA has indicated that they are under development.<sup>62</sup>

## Pooling Samples

Regulators have also struggled with evaluation of testing samples in “pools”, and to-date, only two organizations have been authorized to use this method.<sup>10,11</sup> Pooling samples involves combining more than one sample together and testing it as if it were one sample. For example, under one pooling protocol, known as the Dorfman protocol, if the result of a pool of tests is negative, then all of the samples are considered negative. If the pooled sample comes up positive, then all of the samples in the pool are retested individually to identify the positive individual. Pooling is viewed as a good method to conserve resources because in low prevalence areas, it will reduce the number of tests that are eventually run. However, pooling raises the concern that combining multiple samples may dilute any true positive samples to the point that it will be below the limit of detection. If the quantity of sample is below the limit of detection, then high rates of false negatives from using particular pooling protocols are a concern.

Both pooling samples and asymptomatic testing are likely to be of growing importance as the focus of testing shifts. To a large degree, most testing has been aimed at testing people who have symptoms or who have been exposed to someone with COVID-19. But as the focus moves toward rapidly identifying infected individuals so that they do not return to jobs or schools while they are infectious, testing capacity will need to be expanded to accommodate repeat testing of many asymptomatic or pre-symptomatic individuals. Some studies have suggested that workplaces and schools should be testing everyone at least once a week to detect asymptomatic infections before they trigger significant outbreaks. Just as there will need to be a way to ensure that tests can reliably detect asymptomatic infections, some form of pooling will probably be necessary to ensure that these far larger numbers of people can be tested within reasonable timeframes.

## *Capacity and Utilization*

Once tests have been granted authorization for use, there are a number of challenges to scaling up use and enabling the information they provide to be utilized effectively. There will be a number of critical components to successful implementation of testing strategies, including machines, supplies, data systems, and people. The following section describes where there have been hurdles to implementing effective test strategies, as well as areas that will need to be addressed for future success.

### **Manufacturing and Supply Chain Issues**

Once a test has been developed and validated, production of the tests and reagents need to scale quickly. However, this process can be challenging because of the difficulty in sourcing materials for the test and in anticipating current and future demand. For many manufacturers, once a test has been authorized, quickly expanding the volume of product produced and establishing a distribution chain will be the next step. But the needed materials are often sourced from a number of different locations, and in many cases, needed parts come from organizations outside of the US. Getting supplies from abroad can be a challenge because the pandemic has disrupted the ability to produce goods that rely on people working closely with one another. There may also be higher than normal demand coming from other companies or other countries, which further slows acquisition of supplies.

Test manufacturers often provide two different products: the machine, or platform, that is used to run different tests, and the test kits, which contain various components and that can sometimes be modified by laboratories to run on different platforms. In addition to challenges in acquiring supplies for manufacturing kits, some manufacturing processes are specialized or require protected intellectual property, so cannot be easily replicated in other locations. In the case of high throughput machines, it may take on-site assembly from a specialized team of individuals, limiting the ability to scale-up through traditional processes.

Manufacturers also may face uncertain demand for their testing platforms, leading to financial risk associated with substantial increases in manufacturing capacity. To-date, there are more than a hundred molecular diagnostic tests available, creating a lot of competition for individual test manufacturers. Established manufacturers already have hospital customers for other types of tests run on their platforms, but if there are shortages, these hospital laboratories might purchase new equipment to expand capacity. There is uncertainty about how long this demand will last, and whether manufacturers will have a sustained competitive advantage if they meet short-term demand. All of these factors reinforce the reasons that manufacturers may be dissuaded from making further investments in testing capacity and production.

### **Assessing and Building Needed Laboratory Capacity**

According to many estimates, the US will need to perform millions of tests per day to better control and reduce outbreaks. Expanding the number of tests performed requires increasing the capacity to run tests, which means not only having the tests, but also having the appropriate laboratory space to run them. Laboratories also need to have an adequate workforce to process the tests in a timely manner.



Although testing is more accessible than it was at the start of the pandemic, there are not currently enough tests to screen everyone in the US repeatedly. Testing will need to be prioritized to target areas where people are of greatest risk of serious disease or of infecting large numbers of other people. At present, vast areas of the country fall into this category.

Part of the challenge in developing testing capacity has been understanding and predicting demand for testing products. Due to the absence of a federal testing strategy, demand for tests has been variable among states, and has fluctuated as different areas have experienced surges in infections or have experienced shortages in materials needed for a particular manufacturer's test. While there have been guidelines in place for when molecular diagnostic tests can be used, there has been less guidance for using serology tests, in part because they cannot be used for diagnosis. As a result, many physicians do not see the value of these tests and do not prescribe them for patients. In some cases, academic laboratories may be able to provide capacity for systems overburdened by the volume of test samples coming in. There have been several examples of these types of laboratories developing test protocols and converting space to accommodate testing, but these efforts have not been without challenges.<sup>63,64</sup> Two key aspects need to be addressed before academic laboratories can make a significant contribution to capacity: having data systems to transmit testing results between the laboratory and healthcare provider, and having a system to enable laboratories to bill insurance companies for the tests that they run.<sup>65</sup>

Future demand for tests will also depend on how quickly the pandemic can be controlled. Commercial testing facilities, hospitals, and public health departments might view the current surge as temporary. If strategy is based on such thinking, it is likely that there will be reluctance to make capital investments in testing platforms, create new laboratory space, or hire additional staff. As a result, laboratories will continue to experience a backlog in tests, delaying time to results, and exacerbating the current testing crisis. The current laboratory testing conditions are not sustainable, but policies are not being put in place to ease testing burdens.

## Connecting Data Infrastructure

The road from sample collection to obtaining a test result can often be long. A person concerned about infection might drive to a testing center for sample collection, then the sample is transported to a laboratory for processing, the test result is transferred from a laboratory to a healthcare provider and patient, and eventually on through the public health system. Data must be transferred at each step to ensure that the right test result is connected with the right patient, and reported properly to the state and then the federal government. However, the infrastructure needed for smooth data transfer and sharing is frequently lacking.

For tests that rely on laboratory processing, there are two primary challenges. One is collecting all of the needed data at the outset, which can include the name, address or home location, and demographic information of the person being tested. This information is collected by the healthcare provider who is administering the test, and the laboratory has limited ability to fill in any missing information. But it is the laboratory that must transfer these data to the state with the test results, and if the information is lacking, the data that the state receives will be incomplete.

There have also been data transfer issues that arise from a lack of interoperability between the laboratory information system (LIS) and the electronic health record (EHR) systems. Without interoperable systems, additional inefficiencies are introduced into the process, potentially delaying the reporting of results. And with the recent changes in how data is reported, moving from data transfer from CDC directly to HHS, there have been reports of extreme backlogs, since electronic transfer of data is not possible in many locations and results instead must be faxed in.<sup>66</sup>

## Data Reporting Hurdles

Metrics related to testing have played and will continue to play a critical role in key decisions around reopening and resource distribution. Early on, confirmed cases provided limited insight into where the virus was spreading, but by May, per capita testing levels were a major factor in state reopening plans. Other testing-based measures, such as diagnostic test positivity rate, are being used to determine whether schools can reopen with in-person instruction.<sup>67,68</sup> Testing data supports contact tracing efforts and helps to appropriately allocate resources across different regions. In addition, some test data that are not currently reported, such as time to results, may be helpful in assessing the feasibility of contact tracing.

Despite the critical importance of testing data, data availability and quality are lacking. Many important measures are not being reported by the CDC or the states. There are also no data standards for reporting of variables. Concerningly, the total number of published tests are inconsistent between what the CDC and the states report, raising questions around the reliability of the data.

Data issues will only get more complex with increased screening at POC, including at schools and work, because there is a lack of reporting infrastructure. Currently reported data are from tests used for the purpose of diagnosis. But with school and work reopening plans, testing will increasingly be used for the purpose of surveillance and screening. Screening tests produce near instantaneous results, but the analyzers that produce the results are not always connected to data systems, making this testing information very hard to track without concerted effort. Policymakers will need to evaluate the importance of these screening data (in contrast to diagnostic data described above) to the overall pandemic response and decide on how much to invest in ensuring that they are collected and reported. This issue will likely take on additional relevance in the context of payment for these tests, as is described in the following section.

## Payment and Access

While most tests performed to date have been paid for through the government or insurers, new uses for these tests and the scale of testing needed will introduce significant financial burdens, and it is unclear who will be covering the costs. This section will describe emerging challenges in test coverage, payment, and access.

## Financing Surveillance Efforts

Payment challenges and potential solutions will be closely linked to testing strategies and the purpose behind testing – for example, diagnosing illness in an individual before a medical procedure versus testing as part of a return-to-work or return-to-school strategy. Frequent testing of asymptomatic individuals for the latter purpose will start off being costly, but the price may decrease over time. As testing strategies evolve to include more screening- and surveillance-focused measures, different stakeholders and policymakers are likely to continue to disagree about critical reimbursement policy.

Routine screening of asymptomatic individuals, which forms the basis of many reopening and back-to-work testing strategies, is unlikely to be paid for by insurers, although some Democrats suggest that such payment was intended in the CARES Act. Alternatively, it may be paid for by employers, as the White House interprets the CARES Act mandate. As of publication of this brief, this issue has not been resolved. In this case, federal funding for high-risk public health settings may be required (e.g. nursing homes and public schools).

Given the large number of tests that will be required for widespread screening and frequent testing of asymptomatic individuals, conventional fee-for-service reimbursement for testing will become very costly overtime.<sup>69</sup> Fee-for-service payment models often do not directly link to the quality of a test, nor does such payment require that evidence be generated as to the test's accuracy. Population-based payment models may improve access while controlling spending. Outcomes-based contracts, often relevant for emerging technologies, may reward innovation by using the “best tests” and evidence generation while supporting competition. A value-based payment arrangement may address some of the significant quality and access issues with mass testing in a fee-for-service environment.

## Patient Billing

Despite the federal mandate for 100 percent coverage of testing with no consumer cost-sharing, and the apparent compliance by insurers, ever-evolving testing guidelines are leading to inappropriate patient billing. The CARES Act doesn't identify a specific set of clinical guidelines to follow, such as the CDC guidelines, and states' contradictory and changing guidelines about who should be tested continually alter the conditions for tests to be covered by insurance. Generally, early in the pandemic, limited testing resources were rationed and only symptomatic individuals received tests. Over time, as testing capacity has increased, guidelines have expanded to include more populations and types of testing. For example, in Indiana, and in cities such as Los Angeles, tests are now offered to anyone who seeks them.<sup>70,71</sup>

In the resulting confusion, insurance companies have sometimes billed patients not only for SARS-CoV-2 testing, but also for other tests performed on them in healthcare settings to rule out conditions other than COVID-19. In nursing homes, CMS has required regular employee testing, but it is unclear whether this testing should be paid for by the employer or insurer, sometimes resulting in bills for the employee.<sup>72</sup> Coding errors have also led to inappropriate billing. Future legislation should clarify how broadly the ban on consumer cost-sharing applies, as well as the policies that insurance companies must follow around testing amid the public health emergency.

## Coverage for Asymptomatic Testing

Coverage for testing of asymptomatic patients is politically contentious and receives significant attention as it relates to potential national reopening strategies. Guidance from the Trump Administration issued on June 23, 2020, states that the Families First Coronavirus Response Act guarantees coverage for medically necessary tests only, with or without a prescription – thus covering tests used for an individual's diagnosis or treatment, not for screening or surveillance measures.<sup>73</sup>

Many groups have weighed in with their opinions on this guidance, suggesting that limiting tests to those of medical necessity will undermine the objective of widespread testing for the purposes not just of diagnosing illness, but also to ensure safety amid economic reopening. Democratic leaders of key Congressional health committees disagree with this interpretation, but have nonetheless requested updated guidance more in line with legislative intent to support access to broad testing.<sup>56,74</sup> The American Clinical Laboratory Association has also expressed concern that this guidance opens up a significant coverage gap and leaves laboratories at risk of covering crucial testing, like return-to-work screening.<sup>75</sup> This organization has called upon Congress to provide funds to fill this coverage gap, not necessarily to require coverage from health plans. Payment for non-medically necessary tests will likely evolve with national reopening strategies, testing campaigns, legislation, and federal guidance.<sup>76</sup>

## What is the Way Forward?

As of August 2020, the course of the COVID-19 pandemic in the United States, and the world, remains highly uncertain. Case counts are soaring across much of the US. Community spread in many regions has been extensive, calling into question the feasibility and utility of carrying out widespread testing and linking it to effective contact tracing strategies. And as noted above, evidence that the presence of antibodies in the blood post-infection is short-lived may decrease the utility and importance of serology testing.

At the same time, in the absence of effective COVID-19 vaccines, widespread and frequent testing, along with physical distancing, regular handwashing, regular disinfection of surfaces, and the wearing of masks, remain the only tools available that can enable worksites, schools, and other venues to reopen safely. In effect, the US and many nations face a Hobson's choice on testing, which is to say no choice at all, except to continue it and drastically expand and improve it.

Successful testing strategies are dependent on the cooperation and collaboration of a number of stakeholders. The federal government will need to set clearer guidelines on what tests to use and when. It should also take on a far larger role in directing the distribution of needed supplies, and should appropriate funds for screening tests used for back to work and school efforts. There will also need to be better communication between the federal and state governments to align on standards and reporting. Importantly, additional clarity and regulations will be needed to facilitate rapid and on-site testing for places of employment and education.

Commercial, hospital, and public laboratories will also be important partners in the implementation of national and state testing strategies. A strong commitment to maximizing capacity through additional equipment purchases and increased staffing is needed. Additionally, healthcare providers will need to work closely with laboratories to develop flexibility in where samples are sent for processing to ensure that there is not a backlog in one facility and open capacity in another. Enabling this flexibility will likely require federal coordination to assess overall capacity.

Information on the availability and types of tests for SARS-CoV-2 and COVID-19 must be disseminated broadly to the public to assist people in gaining access to tests. Schools, universities, and employers of all types will need proper guidance and incentives to make sure that testing is administered in a way that keeps people safe and identifies positive cases quickly. Federal and state governments, as well as the CDC, should provide clear guidelines on who should have priority access to available tests. Coordination on all levels is urgent and critical, and public dissemination on testing information and availability will also be important for test access.

As a result of all of these considerations, this paper identifies the following issues as critical for improving the nation's testing response:

1. A far more robust federal strategy for coordination of testing protocols and resources, as well as data standards, is needed. In the absence of a directive articulating a federal testing approach, states and localities will continue to have lead responsibility for testing strategies, including developing frameworks to guide frequency of testing and prioritization guidelines. In addition, stronger federal efforts to procure, and possibly to facilitate production of, testing supplies are needed as shortages of testing components continue in pockets across the country.
2. Specific testing strategies will need to be adjusted based on population and location to ensure rapid expansion of capacity and faster turnaround times to results. Policymakers should consider a number of factors in their strategies, including disease prevalence, needed time to results, reliability of results, and feasibility of employing rapid screening or pooled testing in certain contexts.
3. Reliable data reporting is critical to assess outbreaks, progress, and distribution of resources, but additional efforts are needed at the federal and state levels to ensure consistency in data components and information transfer. In addition, as resources shift to rapid testing, stakeholders need to develop plans for reporting the results of routine screening tests.
4. Given the large number of tests that will be required for widespread screening and frequent testing of asymptomatic individuals, reimbursement at current rates will become very costly over time, and new financing mechanisms for testing should be considered. Future legislation should not only provide funding for testing, but should also address what portion of the cost should be borne by consumers, if any.
5. The science behind asymptomatic infection is still not well understood, and this lack of knowledge has implications for both diagnostic testing and routine screening, especially on whether there will be consistently detectable virus or antibody levels. While FDA recently added information on how to validate molecular and antigen tests for asymptomatic testing, strategies to efficiently validate tests for routine, repeated screening of asymptomatic individuals should be a priority, which will require additional resources for research and regulation to ensure that safe and effective tests get to market faster.

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