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COVID-19 Testing: Key Issues

The COVID-19 pandemic is affecting communities throughout the United States, with the country reporting the highest number of cases and deaths from the disease globally. Containment and mitigation efforts by federal, state, and local governments have been undertaken to "flatten the curve"—that is, to slow widespread transmission that could overwhelm the nation's health care system.

Diagnostic testing is a critical part of the clinical management of COVID-19, caused by the SARS-CoV-2 virus. In addition, both diagnostic and serology testing at scale may be a key component of efforts to ease mitigation measures prior to the development, manufacture, and broad distribution of a vaccine or effective therapeutic. Efforts in the United States to rapidly develop, scale up, and disseminate testing for COVID-19 have faced challenges, including supply chain issues; a shifting regulatory landscape; a lack of consensus around federal coordination of or strategy for testing; concerns with the accuracy of both molecular and serology tests; an early lack of data on test results and capacity; and a delayed ramp-up by commercial laboratories and test manufacturers of both centralized and point-of-care testing. In addition, manufacturing and quality issues with the nation's initial test—developed by the Centers for Disease Control and Prevention (CDC)—resulted in significant delay in early access to testing throughout the country. For more information, see CRS Report R46261, *Development and Regulation of Domestic Diagnostic Testing for Novel Coronavirus (COVID-19): Frequently Asked Questions*.

U.S. Laboratory Infrastructure

Public health testing may be used to help identify and contain the spread of a novel pathogen early in its introduction into the country, as well as to detect and monitor ongoing outbreaks. This testing relies on the CDC and the U.S. network of state and local public health laboratories, including some Department of Defense and international laboratories. In contrast, clinical diagnostic testing is carried out by a number of facilities, including private commercial laboratories (e.g., LabCorp); hospital and other clinical laboratories; and laboratories in academic medical centers and universities. These two systems, while overlapping and connected, have distinct purposes. Clinical testing may be centralized—a sample is collected and sent to a central laboratory for testing—or decentralized, or occurring at or near the patient or point of care, commonly referred to as point-of-care testing.

Diagnostic testing for COVID-19, in part because it is caused by a novel pathogen, was initially carried out by the country's network of public health laboratories. However, it is generally not the role of the public health laboratories to carry out the large-scale clinical diagnostic testing needed during a pandemic response, and demand outstripped supply quickly as the country transitioned to community spread. The commercial sector—including commercial laboratories and commercial test kit manufacturers—as well as clinical laboratories in hospitals and at universities are seen as critical to achieving the scope of testing needed during the COVID-19 public health emergency. Despite ramping up capacity across U.S. laboratories of all types, the country's network of laboratories continues to face challenges meeting the unprecedented demand for testing, in terms of volume, speed, and accuracy. Currently the country performs approximately 150,000 tests per day, and a significant increase in capacity would likely require additional infrastructure (more testing platforms, standing up additional laboratory facilities), in addition to maintaining testing at full current capacity.

Types of COVID-19 Tests

Testing for COVID-19 currently involves both molecular tests and immunoassays. Diagnostic testing for COVID-19 generally relies on *molecular* tests that use nucleic acid amplification techniques such as polymerase chain reaction (PCR) to detect viral genetic material. These tests identify viral nucleic acid in samples taken from individuals' noses or throats using swabs. This type of test is technically complex but well-characterized, generally requiring both specific instruments and highly trained laboratory personnel. PCR tests may be high-throughput, so many samples may be run simultaneously, but the run time is generally several hours. PCR tests may be laboratory-developed tests (LDTs), test kits, or point-of-care tests. Point-of-care tests are usually faster and simpler to run, but often only run a single or a few samples at one time.

COVID-19 testing may also be carried out using *immunoassays*. This type of test detects immune system proteins made by the host (antibodies) or viral components that stimulate the host's immune response (antigens). Tests that detect antibodies in the blood are called serology tests, and they generally indicate either late active infection or exposure to and recovery from prior infection. Serology tests are not generally used alone for diagnosis of disease; rather, they may sometimes be used in combination with a molecular test for diagnosis. Serology testing also may be used to identify individuals who can donate convalescent plasma as a possible therapeutic; to help guide development of a vaccine; and to determine the extent and spread of COVID-19 in the general population, as well as the infection fatality rate. Rapid antigen tests—which have not yet been authorized for use in the United States for COVID-19—can detect viral antigens, generally in a throat or nose swab. These tests are usually point-of-care, low-cost, easy to use, and used for diagnostic purposes. However, these

tests in particular tend to have lower accuracy than molecular diagnostic tests.

FDA Emergency Use Authorization (EUA) Guidance for COVID-19 Testing

Through guidance, the Food and Drug Administration (FDA) has allowed for modifications to the usual EUA process to facilitate a more rapid scale-up of testing. On February 29, FDA announced a policy which allows laboratories that have developed and validated their own COVID-19 diagnostics to begin using the tests prior to receiving Emergency Use Authorization, as long as the laboratory notifies FDA and submits EUA materials within 15 days. This guidance was updated on March 16 to apply similarly to commercial test kit manufacturers, allowing them to market test kits prior to receiving EUA. The agency also allowed tests to be used and marketed without EUA in two cases: (1) where states have authorized laboratories to carry out testing within the state and (2) for serology tests where the manufacturer notifies the agency and labels the test as required by the guidance. The agency reports that more than 100 serology tests are currently being marketed without EUA; serology tests may also be brought to market under an EUA, and several have been. In addition, any at-home test or self-collection of a specimen at home would need to have authorization prior to marketing. The agency has not yet authorized any at-home COVID-19 test. It did grant authorization for the first at-home self-collection kit for use with LabCorp's PCR test.

CLIA and the COVID-19 Pandemic

All clinical laboratories in the U.S. need to receive CLIA (Clinical Laboratory Improvement Amendments) certification in order to test human samples for purposes of clinical diagnosis and treatment. Many questions have arisen during the COVID-19 public health emergency about possible flexibilities in CLIA requirements, for example, with respect to the certification process or personnel qualifications, as well as the use of temporary testing sites. The Centers for Medicare & Medicaid Services (CMS) has issued guidance to provide some flexibility with respect to CLIA requirements using its enforcement discretion. In particular, CMS clarifies that testing may be performed at designated overflow sites and that laboratories may begin testing upon receiving a CLIA number, but prior to receiving a paper certificate.

Accuracy Concerns with COVID-19 Testing

Accuracy concerns have arisen with respect to both molecular diagnostic and serological COVID-19 testing. It has been reported that PCR tests for COVID-19 may return as many as 30% false negatives (a negative result, where the individual is a true positive). While no diagnostic test performs with perfect accuracy, certain issues may result in lower accuracy. PCR-based tests are generally very accurate, but problems can occur with sampling technique, storage and transport, and the extraction step. In addition, viral load varies during the course of an infection and can affect the amount of virus in a collected sample.

Serology tests authorized by FDA generally have high sensitivity (ability to detect a true positive) and specificity (ability to detect a true negative); their accuracy may vary based on the prevalence of the infection in the tested population. In addition, technical issues such as cross-reactivity with antibodies from commonly circulating coronaviruses can return false positives. Serology tests are allowed to be marketed and used without an EUA, creating further unknowns about performance of these tests. The FDA is working with other federal agencies to provide voluntary validation for these tests.

Supply Chain and COVID-19 Testing

Supply chain issues related to COVID-19 diagnostic testing have affected access to testing nationally. As the FDA has granted EUAs for more LDTs and test kits—including point-of-care tests—and testing volume has increased, laboratories across the country have reported shortages in necessary supplies. PCR testing involves sample collection, nucleic acid extraction, and testing to identify presence of the SARS-CoV-2 virus. Supplies needed for each of these steps have been in shortage, including swabs needed for sample collection; viral transport media needed to stabilize and store the sample after collection and during transport; RNA extraction kits and reagents needed to extract viral RNA from the sample prior to testing; and instruments, test kits, and testing reagents needed to amplify and detect viral nucleic acid. Personal protective equipment (PPE) needed during sample collection has similarly been in short supply.

These shortages have been anecdotally reported by laboratories, and were documented in an April 3 report by the Department of Health and Human Services Office of the Inspector General addressing hospitals' experience responding to COVID-19. The report notes that "severe shortages of testing supplies and extended waits for test results limited hospitals' ability to monitor the health of patients and staff." FDA has worked with industry to try to identify and mitigate shortages through modifications to test EUAs that allow for the use of alternate supplies when carrying out a test and the establishment of an industry hotline for device shortages. However, shortages reportedly persist due to global demand and the unprecedented level of testing, as well as a lack of coordinated ascertainment, production, and allocation of supplies, and the FDA does not have the authority to allocate or distribute supplies.

Serology Testing to Determine COVID-19 Spread in the United States

Many cases of COVID-19 are reportedly mild or asymptomatic, and therefore go undetected. As such, widespread serology testing would help to characterize the scope and extent of the disease in the United States. CDC reported in late March that the agency is in the early stages of beginning serosurveys—surveys that measure the proportion of a population that has antibodies to an infection—to gauge the spread of COVID-19. The first of these studies is already underway in six major metropolitan areas, including New York City and Seattle, and it aims to "monitor how many people develop SARS-CoV-2 antibodies over time." NIH also recently reported it has undertaken a large serosurvey to determine how many healthy adults have been exposed to COVID-19.

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