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Identifying and isolating active cases in the United States

Identifying and then isolating people infected with coronavirus reduces the likelihood of a COVID-19-negative individual coming into contact with an active case.

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This document provides an overview of the different types of testing available, what their strengths and limitations are, and some examples of use cases for each. It provides information to workplace leaders who may want to consider investing in interventions for identifying and isolating active cases to help keep employees safe. While there is no single "silver bullet" solution for all workplaces, the following information can be used alongside guidelines from local and national health authorities to develop the right strategy for protecting a workforce.

Recent studies show that 40 percent of people who test positive for COVID-19 do not have symptoms but may still be contagious. This creates considerable risk of continued disease spread in the workplace if asymptomatic and presymptomatic carriers go undetected.[1] There is much debate about what constitutes the "right" level of testing. We conducted an in-depth review and simulation of how different testing volumes and performance levels could reduce transmission rates for a given population. Analysis and modeling suggest that widespread testing with rapid results—even at current levels of accuracy—could likely curtail transmission of COVID-19, reduce hospitalizations and deaths, decrease days of lost productivity, and support an accelerated full "reopening" of the economy.

Modeling suggests that investing $5 billion to $20 billion in testing volume each month could restore $140 billion to monthly GDP. This level of testing is in line with or slightly above other consensus estimates, including the Brookings Institution and Harvard Global Health Institute, and somewhat lower than the high-end estimates by Harvard's Edmond J. Safra Center for Ethics.[2]

Testing is expanding, but not at consistent levels across municipalities, counties, states, or nations. Many programs still lag behind the testing levels recommended by experts.[3] Diagnostic and screening tools were in short supply early in the pandemic, and as case counts and infection rates rise again, supply shortages once more pose a challenge.

Isolating infected people and contact tracing remain a challenge to deploy at scale:

— Some states have increased measures to restrict activities for their citizens.

— Growing public fatigue with health measures and mixed messages about those measures may impact public willingness to isolate after testing positive.

— The United States has yet to deploy contact tracing at scale. While several states have technological solutions, they are opt in, and participation remains low. The primary approach to contact tracing relies on an infected person providing a recent history of interactions and contacting the people involved, which becomes more difficult at higher positivity rates, which are currently in excess of 10 percent.[4]

[1] Matt Feaster and Ying-Ying Goh, "High proportion of asymptomatic SARS-CoV-2 infections in 9 long-term care facilities, Pasadena, California, USA, April 2020," *Emerging Infectious Diseases*, October 2020, Volume 26, Number 10, pp. 2416–19, cdc.gov.
[2] "Testing responses through agent-based computational epidemiology (TRACE)," The Brookings Institution, brookings.edu; "As COVID-19 outbreaks grow more severe, most U.S. states still fall far short on testing," Harvard Global Health Institute, June 30, 2020, globalhealth.harvard.edu; "Appendix: Estimates of required COVID-19 testing for the US," in *Why we must test millions a day,* COVID-19 Rapid Response Impact Initiative White Paper 6, Harvard University: Edmond J. Safra Center for Ethics, April 8, 2020, ethics.harvard.edu.
[3] "Which U.S. states meet WHO recommended testing criteria," Johns Hopkins University of Medicine, February 2, 2021, coronavirus.jhu.edu.
[4] Paresh Dave, "Virginia touts nation's first contact tracing app with Apple–Google tech," Reuters, August 5, 2020, reuters.com.

The analysis below focuses on five ways to isolate active cases:

— Nondiagnostic individual screening

— Lab-based individual diagnostics

— Point-of-care (POC) rapid individual diagnostics

— Serological testing

— Broad monitoring

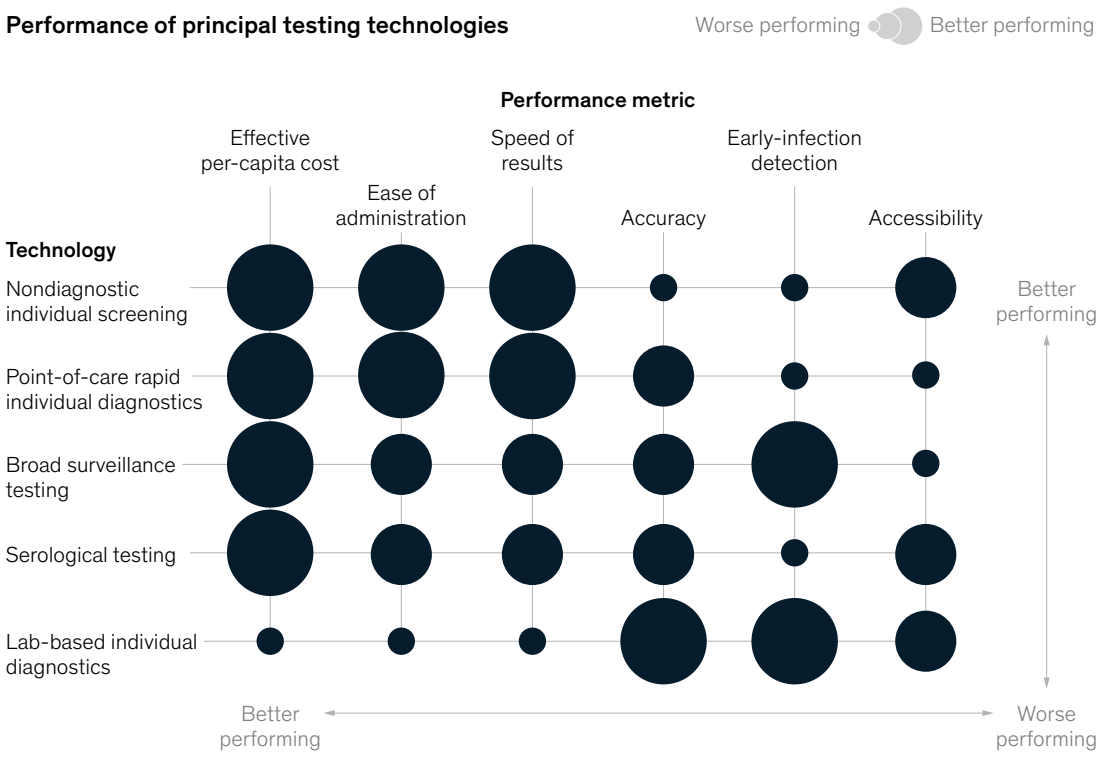
Each approach has strengths but also limitations, as summarized below. The technologies employed perform differently, their costs and availability vary, and not all of them fit every environment or workplace. The assessment below is based on population at large; there may be additional challenges facing vulnerable populations such as reduced access to even basic testing technologies (Exhibit 1).

Nondiagnostic individual screening

Screening uses noninvasive technology to check for the presence of symptoms that may indicate the virus, rather than checking for the presence of the virus itself. Commonly used screening tools include temperature checks using a contactless instant-read thermometer as people enter a building or room and apps that prompt people to report symptoms and recent interactions.

Exhibit 1

Wide-ranging variations in the capabilities of available testing technologies should be considered when selecting appropriate technologies.



Limited accuracy and ability to detect early infections mean that nondiagnostic individual screening may help build public confidence but may not reduce disease spread when used alone.

Strengths include the following:

— *Low cost.* Instant-read thermometers can be purchased in local retail stores for about $40 to $60 each and can be used many times over, with recurring costs limited to the cost of batteries.

— *Speed of results.* For temperature checks, readings are instantaneous.

— *Ease of administration (minimal training required).* These devices can be purchased over the counter and used by any individual.

Limitations include the following:

— *Accuracy.* Temperature screening is predicated on a high fever being a reliable sign of infection, but not every COVID-19 infection causes a fever.[5] Self-reporting apps rely on a person's ability—and willingness—to recognize and accurately report symptoms.

— *Effectiveness of early detection.* Early temperature screening ignores the fact that fever may occur later in infection, after a person becomes contagious.[6] Self-reporting of symptoms is similarly limited, as many of the best-known symptoms appear some 12 days after infection, well into the period when people are contagious.[7]

Lab-based individual diagnostics

Today, lab-based diagnostics are the most widely used individual COVID-19 diagnostics. The technologies employed include the most sensitive diagnostics available—among them, the CDC RT-PCR diagnostic panel that is the "gold standard" against which other tests are measured.[8] The technical accuracy of these technologies accounts for the popularity of lab-based diagnostics, public trust in their results, and the ongoing development of the technologies.

The lab-based tests take two forms—molecular and antigen (used primarily at POC, as described below).

Molecular tests like the RT-PCR panel are the most common, sensitive, and accurate tests because they deliver accurate results by selectively amplifying and identifying COVID-19 RNA. They can be challenging to scale and execute at the levels needed for broad, proactive screening every week. According to Johns Hopkins, in November, the United States was testing at a rate of about eight million a week, below the estimated capacity of ten million to 12 million. RT-PCR tests face raw-material constraints (for example, reagents), relatively high costs ($100 to $125 per test), and the need to pair a sample with a lab that can process the test quickly.

Lab-based individual diagnostics include both "closed system" and "open system" lab tests:

— Closed system tests are proprietary, require specific materials available from just a few qualified vendors, and can run only on a short list of compatible equipment.

— Open system tests can use reagents from a number of vendors and can run on a variety of compatible equipment.

Lab-based diagnostics will likely remain the primary way to verify an infection because they are more accurate and have lower detection thresholds and higher throughput than other diagnostic technology. However, the turnaround time for lab-based diagnostics is long—at least 24 hours when

[5] "Coronavirus symptoms: Frequently asked questions," Johns Hopkins Medicine, October 2020, hopkinsmedicine.org.
[6] James Hamblin, "Paging Dr. Hamblin: Everyone wants to check my temperature," *Atlantic*, August 12, 2020, theatlantic.com.
[7] Jina Ko, Hakho Lee, Mikael J. Pittet, and Ralph Weissleder, "COVID-19 diagnostics in context," *Science Translational Medicine,* June 2020, Volume 12, Number 546, stm.sciencemag.org.
[8] "CDC diagnostic tests for COVID-19," Centers for Disease Control and Prevention, August 5, 2020, cdc.gov.

a lab is working at peak efficiency. Sample pooling may improve the cost and availability of lab-based diagnostics, but no at-scale examples of effective pooling strategies have emerged to date (Exhibit 2).

Strengths include the following:

— *Effectiveness in early detection.* According to the FDA's Reference Panel, of all testing technologies, molecular PCR has the lowest detection threshold because of the amplification step. While few tests are approved for use on asymptomatic people, many have been used off label to test people who have known exposure to COVID-19 or other concerns about their infection status, and the tests have detected some early infections.[9]

— *Accuracy.* Manufacturers advertise that the accuracy of molecular tests exceeds 90 percent in terms of sensitivity (true positive rate) and specificity (true negative rate). Accuracy achieved in the clinic is typically about 70 percent.[10]

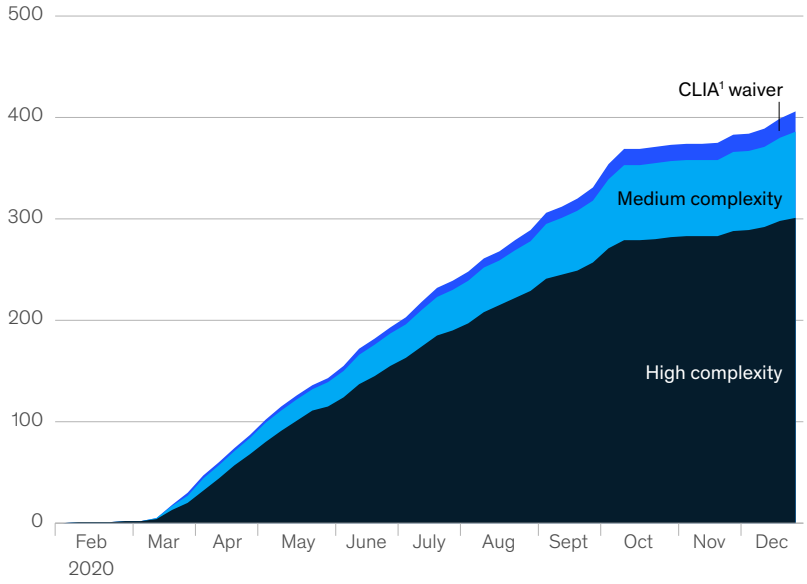
Limitations include the following:

— *Ease of administration.* Lab-based molecular tests have a complex value chain—samples must be collected by professionals, stored securely, transported to a lab, prepped for

Exhibit 2

Emergency Use Authorizations for COVID-19-testing technologies increased gradually since the pandemic started, but the growth rate has slowed.

FDA Emergency Use Authorizations granted for COVID-19-testing technologies, by date of initial approval



[1]Clinical Laboratory Improvement Amendments.
Source: FDA, as of Jan 14, 2021

[9] Greg Slabodkin, "Hologic receives FDA emergency use for asymptomatic COVID-19 test," MedTech Dive, September 28, 2020, medtechdive.com.
[10] Ramy Arnaout et al., "SARS-CoV2 testing: The limit of detection matters," bioRxiv, June 2020, ncbi.nlm.nih.gov.

analysis, and run through a complex machine operated by a professional. Both sample collection (for example, with a nasopharyngeal swab) and test administration require special training and qualifications.

— *Speed of results.* The complexity of the value chain, proximity to a lab, and the capacity and throughput of the lab all contribute to the speed of results from lab-based molecular tests. These tests take the longest time from sample collection to receipt of results. Early in the pandemic, lab-test turnaround times in the United States exceeded seven days, which increased public uncertainty about how to behave while waiting for results and increased the likelihood that infected individuals spread the infection to others between sample collection and receipt of results.[11]

— *Cost.* These tests typically cost $100 to $125.[12] At the lower end of the price range are tests offered by high-volume providers; at the higher end are swab-at-home kits. The cost makes large-scale, high-volume testing prohibitive for many organizations and localities. It can also be a potential barrier to access for vulnerable populations.

Point-of-care rapid individual diagnostics

POC testing involves technology similar to lab-based testing but employs smaller, easier-to-use equipment and typically analyzes a single sample at a time. POC testing is more commonly in use in smaller clinics and hospitals that do not have labs on site (for example, an urgent care center or emergency room). But POC testing has seen less utilization during the pandemic than lab-based testing because it lags in available equipment and throughput.

The technology used in rapid POC testing includes portable tests that leverage the two most common types of underlying technology: isothermal molecular and antigen. Other technologies are in development, and various rapid-development funding efforts have launched, such as the National Institute of Biomedical Imaging and Bioengineering's RADx program.[13] Recently, antigen-based POC testing has become the most readily available rapid-result test, boosted by the US government's purchase of 150 million kits for distribution to schools and nursing homes.

Rapid antigen-based POC tests are relatively simple to construct, are less expensive (less than $5 per test), and can deliver results in about 15 minutes. But antigen tests cannot detect the presence of the virus until the first five to seven days after symptoms appear.[14] These tests do not amplify COVID-19 RNA, so they may miss infections that an RT-PCR test would identify as positive, even soon after exposure when the viral load remains low. Some experts suggest that administering antigen tests several times a week, a strategy called serial testing, could overcome the limitation of antigen tests' high-detection threshold, increasing the effectiveness of antigen testing.[15]

Strengths include the following:

— *Speed of results.* Rapid turnaround, in a matter of minutes, speeds the process of isolating a person who tests positive.

— *Cost.* Rapid tests tend to be more cost-effective than similar lab-based tests ($5 to $25 versus $100 to $125).

— *Ease of administration.* While many tests still require administration and interpretation by a medical professional, the work does not have to happen in a fully staffed lab. A single

[11] Matt Berger, "You now have to wait more than a week for COVID-19 test results—and why it may get worse," *Healthline*, July 21, 2020, healthline.com.
[12] To learn more about tests, visit letsgetchecked.com and healthtestingcenters.com.
[13] "Rapid acceleration of diagnostics (RADx)," National Institutes of Health, December 23, 2020, nih.gov.
[14] "SARS-CoV-2 antigen testing in long term care facilities," Centers for Disease Control and Prevention, January 7, 2021, cdc.gov.
[15] Daniel B. Larremore, Michael J. Mina, and Roy Parker, "Rethinking COVID-19 test sensitivity—a strategy for containment," *New England Journal of Medicine*, November 2020, Volume 383, Number 22, nejm.org.

The production of quantitative antibody tests will be key to evaluating vaccine effectiveness, issuing immunity passports, and tracking progress toward herd immunity.

professional (for example, nurse or technician) working alone can get the job done.

Limitations include the following:

— *Effectiveness early in an infection cycle.* The clinical sensitivity of some molecular tests approaches 70 percent. But antigen tests do not perform as well and have a higher detection threshold (approximately 10^5 to 10^6 copies per milliliter for antigen versus approximately 10^3 copies per milliliter for molecular).[16] They typically do not detect an infection until four to five days after its start.

— *Extent of use.* Rapid tests have developed more slowly than lab-based tests and account for a smaller portion of tests administered to date. Rapid antigen tests, the most common POC tests, are forecast to deliver 20 to 30 percent of total test volume by the end of 2020.

Serological testing

Serological testing detects antibodies specific to COVID-19 in a person's blood serum. This technology can establish the prevalence of past infections in communities, but it cannot identify active, infectious cases. The body does not produce a detectable level of antibodies until late in the COVID-19 infection.

Antibody tests detect the immune system's response to COVID-19 infection by looking at antibodies that are detectable near the end of a patient's infectious period. The antibodies can last for several months, but the duration of infection resistance remains unclear. The latency of serological tests limits their usefulness for diagnosis or screening to curtail disease spread.

However, antibody testing could play a key role during the later phases of the pandemic by monitoring the immunity developed in communities by vaccination or prior infection. Current research indicates that antibodies provide temporary immunity that likely wanes after several months. The production of quantitative antibody tests will be key to evaluating vaccine effectiveness, issuing immunity passports, and tracking progress toward herd immunity.[17]

Strengths include the following:

— *Cost.* Whether approved for POC use or restricted to lab processing, serological tests are simple to produce and administer, making them a comparatively low-cost testing option.

[16] "SARS-CoV2 testing: The limit of detection matters," June 2020.
[17] James Gallagher, "COVID: Antibodies 'fall rapidly after infection'," BBC, October 27, 2020, bbc.com.

Limitations include the following:

— *Ability to detect early infections.* Serological testing cannot detect active infections.

Broad monitoring

Broad surveillance testing is seeing uptake during the pandemic—notably, downstream wastewater surveillance by multiple municipalities in the United States and upstream wastewater surveillance (see sidebar, "Upstream wastewater surveillance use case"). Downstream testing typically happens at an existing treatment facility where wastewater lines for a municipality converge. Upstream testing typically focuses on a defined population associated with a single building, such as a college dormitory, nursing home, or school.

Surveillance testing can reduce disease spread by identifying asymptomatic and presymptomatic people earlier in the infection cycle. Surveillance testing can also monitor large portions of a population and inform targeted deployment of scarce testing resources, preventing outbreaks earlier and at lower cost.

Reinforcing surveillance, approaches, and tools for tracing the contacts of active cases are evolving:

— Individual interviews are used widely. They rely on an infected person remembering recent interactions so a healthcare provider or public official can follow up with each contact.[18]

— Attendance logging at venues provides a more reliable and comprehensive view of known interactions and enjoys broad uptake by businesses and state policies.[19]

— Generally available automated tracing, as through public smartphone apps, is developing but has yet to secure broad use at scale.[20]

[18] "Contact tracing for COVID-19," Centers for Disease Control and Prevention, December 16, 2020, cdc.gov.
[19] Gabe Guarente, "Washington gives restaurants set of reopening requirements," *Eater Seattle*, May 12, 2020, seattle.eater.com.
[20] "Exposure notifications: Using technology to help public health authorities fight COVID-19," Google, google.com.
[21] Jessica Golden, "Here's the device the NFL and NBA are using for coronavirus contact tracing and social distancing," CNBC, July 22, 2020, cnbc.com.

Upstream wastewater surveillance use case

Upstream wastewater surveillance can enable new disease-management strategies cost-effectively. Unlike traditional wastewater surveillance, which analyzes samples taken from municipal wastewater-treatment facilities that serve very large populations, upstream wastewater testing can detect disease prevalence in populations small enough for cost-effective deployment of policies and practices.

The University of Arizona pioneered a protocol for collecting, preparing, and analyzing upstream wastewater samples for its dorms.[1] When the testing discovered two asymptomatic students in a dorm, the university isolated both students immediately, and no further cases developed. These cases would likely have taken several more days to detect through other on-campus tests that rely on people volunteering for testing based on symptoms.[2]

Diverse institutions, including universities, primary schools, nursing homes, and correctional facilities, have followed the university's lead.

Upstream wastewater testing, in effect, enables surveillance of 100 percent of a target population, with results received in near real time, equipping leaders to adjust policies and practices quickly to manage emerging outbreaks.

[1] "Wastewater testing at UArizona stops coronavirus spread; garners national attention," The University of Arizona, August 31, 2020, west.arizona.edu.
[2] Ibid.

— Small-scale commercial solutions like dedicated digital wristbands or apps targeted to specific operations (for example, a manufacturing facility or a military base) are available, but their utilization is unclear.[21]

Strengths include the following:

— *Cost-effectiveness.* Surveillance testing spreads the cost of a test over a large population. Deployed effectively, this testing can relieve the burden on individual diagnostics for understanding the prevalence of disease and detecting outbreaks early.

— *Ability to detect early infections.* Monitoring approaches like upstream wastewater surveillance can detect infection in asymptomatic people and isolate them before it spreads widely.

Limitations include the following:

— *Extent of use.* Surveillance testing is not yet used widely at a national level in the United States.

Moving to action

The overview of testing types outlined in this article can inform how testing could be included in a return to workplace strategy for organizational leaders. For additional information on the technology and performance of these testing types, please feel free to contact us. For further guidance on how and when these tests should be applied, please consult the guidelines provided by your local and national public-health authorities and reach out to them with questions.

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