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To Test, Perchance to Diagnose: Practical Strategies for Severe Acute Respiratory Syndrome Coronavirus 2 Testing

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Testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in symptomatic and asymptomatic patients is an important component of the multifaceted approach of managing the coronavirus disease 2019 pandemic. Determining how to best define testing strategies for different populations and incorporating these into broader infection prevention programs can be complex. Many circumstances are not addressed by federal, local, or professional guidelines. This commentary describes various scenarios in which testing of symptomatic or asymptomatic individuals for SARS-CoV-2 virus (antigen or ribonucleic acid) can be of potential benefit. Consideration to pretest probability, risks of testing (impact of false-positive or false-negative results), testing strategy, as well as action based on test results are explored. Testing, regardless of setting, must be incorporated into overarching infection control plans, which include use of personal protective equipment (eg, masks), physically distancing, and isolation when exposure is suspected.

Keywords. molecular diagnostics; SARS-CoV-2; testing.

Laboratory testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in symptomatic and asymptomatic patients is an important but single component of the multifaceted approach to ending the coronavirus disease 2019 (COVID-19) pandemic. Detection of SARS-CoV-2 antigen (Ag) or ribonucleic acid (RNA) in an individual is a defining criterion for COVID-19 infection. Beyond diagnosis, test results are used to (1) enroll individuals in therapeutic clinical trials, (2) cohort patients within hospitals, (3) inform quarantine decisions, and (4) track the progress of the pandemic. Determining how to best define testing strategies in different populations and incorporate this into broader infection prevention programs can be complex. This document explores various scenarios in which testing of symptomatic or asymptomatic individuals for SARS-CoV-2 virus (Ag or RNA) is of potential benefit. Testing for antibodies against SARS-CoV-2 is not discussed, but guidance is available elsewhere [1, 2]. These case studies provide general guidance only and are likely to change as the pandemic evolves. With any test, consideration should be given to the population being tested, the prevalence of disease in the community, the pretest probability, and the goal of testing (detection of all infections vs detection of those most likely to transmit disease to others). As the pandemic evolves, vaccination rates increase and cases decrease, and the strategies discussed herein are likely to change, due to shifting pretest probability from high to low.

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 TESTS

Several classes of tests with US Food and Drug Administration (FDA) Emergency Use Authorization (EUA) are available to detect SARS-CoV-2 infection. The majority have been authorized by the FDA for testing of symptomatic individuals only, although some are authorized for use in asymptomatic individuals (https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas).

Nucleic acid amplification tests (NAATs) and Ag tests target the virus

itself, by detecting viral RNA or proteins, respectively. Nucleic acid amplification test formats vary significantly, ranging from complex tests that are performed in a laboratory to those that can be performed outside a laboratory setting, with a Clinical Laboratory Improvement Amendments Certificate of Waiver. Nucleic acid amplification test methods include reverse-transcription polymerase chain reaction (RT-PCR) and isothermal amplification assays. Tests may detect SARS CoV-2 alone or SARS CoV-2 in parallel with other respiratory pathogens. The NAAT and Ag tests are subcategorized by speed of result, with "rapid" tests defined as those providing an answer within 1 hour and standard NAAT taking >1 hour of on-instrument testing time; actual time from specimen collection to results reporting in medical records is influenced by a variety of factors, including specimen transport time, time from arrival in the laboratory to testing, and time from availability of a result to reporting. Most Ag tests are designed for rapid performance at point of care and are referred to as rapid diagnostic tests (RDTs). A comprehensive listing of EUA COVID-19 tests are available from the FDA (https://www.fda.gov/medical-devices/emergency-use-authorizations-medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices).

Specific test performance criteria are described by the FDA for tests that have achieved EUA (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-coronavirus-disease-2019-tests-during-public-health-emergency-revised). Test performance is categorized into analytical and clinical performance. Analytical performance is dependent on intrinsic factors including choice of SARS-CoV-2 targets (viral genes or proteins), analytical sensitivity (based on, for example, nucleic acid extraction and amplification efficiency), analytical specificity, and the impact of genetic mutations

in SARS-CoV-2 targets. Extrinsic factors affecting assay performance include patient population (symptomatic vs asymptomatic, high vs low risk, children vs adults), disease severity, timing of sample collection relative to exposure or symptom onset, sample type, and sample quality. A variety of different specimen types have been used for the diagnosis of COVID-19, and these may impact analytical performance—Infectious Diseases Society of America (IDSA) guidelines include discussion on the clinical utility of different specimens types [3].

Clinical test performance (ie, positive predictive value [PPV] and negative predictive value [NPV]) is influenced by the prevalence of disease in the population being tested. In a high-prevalence setting, it is more likely that individuals who test positive truly have disease (ie, a higher PPV) than if the test is performed in a population with low prevalence. Therefore, PPV is a priori lower for asymptomatic individuals than for symptomatic ones, a factor that must be considered when performing testing on asymptomatic populations.

In general, standard NAAT and rapid RT-PCR tests are more sensitive than rapid isothermal tests or Ag RDTs for symptomatic patients [3, 4]. At the time of this writing, only limited studies have evaluated test performance characteristics when applied to asymptomatic populations [5], and substantial design variability exists in those studies that are available (Supplemental Table 1). In general, viral loads are the same or lower in presymptomatic or asymptomatically infected individuals versus symptomatic individuals, and viral clearance is generally faster (Supplemental Table 1). However, the viral load distribution in populations of asymptomatic individuals is wider than in symptomatic individuals, with lower median values at the time of testing [6–8].

The Centers for Disease Control and Prevention (CDC) guidelines recommend confirmation of negative Ag RDT results with a standard NAAT or rapid

RT-PCR for symptomatic patients with a high index of suspicion for SARS CoV-2 infection [9]. Likewise, IDSA recommends confirming negative rapid isothermal tests by a standard NAAT or rapid RT-PCR for these patients [3, 4].

TESTING OF SYMPTOMATIC INDIVIDUALS

Testing of symptomatic patients for SARS-CoV-2 is a cornerstone of clinical management of infected individuals, and this is discussed extensively in IDSA guidelines, including optimal timing of specimen collection with reference to symptom onset [1]. Testing strategies are summarized from these guidelines in Table 1.

Testing of Patients With New Onset of Symptoms and Confirmed Past Coronavirus Disease 2019 Infection

A common challenge is the evaluation of individuals with new onset of symptoms compatible with COVID-19 and previous history of a positive SARS-CoV-2 laboratory test (Table 2). Individuals may shed detectable SARS-CoV-2 RNA for extended periods postinfection. A recent meta-analysis of 79 studies (5340 individuals) documented a maximal duration of RNA detectability of 83 days (upper respiratory specimens) and 59 days (lower respiratory specimens) [10]. In general, duration of viral detection is shorter for asymptomatic versus symptomatic individuals, but some studies have noted no difference in duration of SARS-CoV-2 NAAT positivity (Supplemental Table 1).

Clinicians desire an objective measure of disease state and infectivity. Although RT-PCR cycle threshold (Ct) values have been used to estimate the amount of viral RNA in the sample, it is critical to understand that current SARS-CoV-2 assays are not standardized to provide a quantitative readout of viral RNA concentration. Limitations to using Ct values for clinical decision making are outlined in Table 3. In general, SARS CoV-2 viral RNA concentration in the upper respiratory tract peaks around time of symptom

Table 1. Summary of Testing Symptomatic Individuals

Goal(s) of Testing
• Diagnosis of COVID-19 infection for patient management including treatment and isolation
• Epidemiological tracking in community
Testing Strategies
Testing performed as early as possible after the onset of symptoms. Standard NAAT and rapid RT-PCR preferred; antigen tests and rapid isothermal assays may also be used but may have lower sensitivity. NP swab considered gold-standard, but alternative specimens may be used if included in the test's EUA or validated by testing laboratory. Testing of lower respiratory tract specimens may be useful for patients with respiratory failure in second week of illness.
Test choice is determined by local test capacity (including availability of supplies).
Positive Result: Confirmed or probable diagnosis of COVID-19. Limited value for confirming positive results by a second test, regardless of method used.
Negative Result: If performed by Ag RDT or rapid isothermal NAAT, consideration should be given to confirming with a standard NAAT, if suspicion for COVID-19 remains high.

Abbreviations: Ag, antigen; COVID-19, coronavirus disease 2019; EUA, Emergency Use Authorization; NAAT, nucleic acid amplification test; NP, nasopharyngeal; RDT, rapid diagnostic test; RT-PCR, reverse-transcription polymerase chain reaction.

onset. Cultivable virus persists up to 10 days in mild-to-moderate disease but may be longer in cases of severe pneumonia and in some immunocompromised hosts [11–13]. Although Ct values appear to correlate with virus recovery in culture [12], efforts to correlate Ct values with infectivity should be interpreted with caution. Viral culture has notoriously poor analytical sensitivity, meaning a negative culture result does not necessarily equate with lack of infectiousness. Furthermore, the impact of monoclonal antibody therapy and immunosuppressive therapies on Ct has not been defined, but it may potentially impact results.

TESTING OF ASYMPTOMATIC INDIVIDUALS

The SARS-CoV-2 control strategies that incorporate testing asymptomatic individuals do not replace other mitigation measures to reduce spread such as appropriate ventilation, masking, physical distancing, hand hygiene, cleaning, and/or cohorting, as appropriate [14, 15]. In addition, laboratories in the United States continue to experience extensive

SARS-CoV-2 staff and testing supply shortages [16]. Diagnostic testing must be prioritized over screening of asymptomatic individuals when supply chain or manpower is uncertain.

Testing Asymptomatic Individuals After a Single High-Risk Exposure

The CDC defines an exposure as household contact or close contact within 6 feet of an individual with confirmed or suspected COVID-19 [17, 18]. Higher risk exposures are defined as follows: those that are prolonged, that is, at least 15 minutes over a 24-hour period; those during which the exposed individual is not wearing a mask or eye protection; those that take place indoors, especially in poorly ventilated spaces; and those in which aerosols are generated, for example, endotracheal intubation. The timeframe for contact includes the 48 hours before the source became symptomatic or, if the source is asymptomatic, before they tested positive for SARS-CoV-2.

Fourteen days of quarantine has been the standard recommendation for exposed individuals, based on the observed

incubation period of the virus [19, 20]. However, a 14-day quarantine period can be impractical in some community and healthcare settings, imposing hardship on individuals who are barred from work or school or leading to staffing shortages in healthcare facilities and other essential workplaces.

The CDC recently published options to reduce quarantine duration for contacts of individuals with COVID-19 [21]. One option allows ending quarantine after as few as 7 days, if the exposed individual remains asymptomatic, and if results of a diagnostic laboratory test for SARS-CoV-2 on a sample collected in the 48 hours before ending quarantine (day 5–7 after exposure) is negative (Table 4). A negative test at this time does not rule out developing infection in the remainder of the 14-day incubation period. Modeling studies have demonstrated that the residual postquarantine risk of transmission through day 10 is 4.0% (range, 2.3%–8.6%) when an RT-PCR test is used and 5.5% (range, 3.1%–11.9%) if an Ag RDT is used. These estimates compare to a median risk of approximately 1%

Table 2. Summary of Testing Considerations for Individuals With New Onset COVID-19 Symptoms Post Recent Confirmed Infection

Goals of testing: Determine whether individual has recurrence of COVID-19 or reinfection
Pretest probability: Low
Testing strategy: Test individual using a NAAT. Evaluation of the Ct value may be considered in very selected cases but there are major limitations to this approach (refer to Table 3).
Positive result: Consider clinical scenario carefully and repeat testing.
Negative result: Patient negative for SARS-CoV-2 detection, consider alternative causes of symptoms, if clinically relevant.

Abbreviations: COVID-19, coronavirus disease 2019; Ct, cycle threshold; NAAT, nucleic acid amplification test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Limitations of Using Ct Values for SARS-CoV-2 RT-PCR Testing

Definition
A Ct value is the number of PCR amplification cycles required to reach a fixed level of fluorescence at which the result of real-time PCR changes from negative (not detectable) to positive (detectable). In general, a higher Ct value indicates a lower viral RNA titer and a lower Ct value indicates a higher viral RNA titer, but these are not quantitative tests.

Cautions
• No COVID-19 test has been validated as a quantitative assay. Ct values can be used as rough estimates of the viral RNA concentration in a specimen only.
• Ct values are "not comparable" from one assay to another.
• Ct values can vary significantly depending on the NAAT, sample type, consistency in sample collection, time from infection to testing.
• There is no international standard by which results from different tests can be calibrated.
• Residual RNA may be detected from nonviable virus.
• When comparing data from different studies, Ct values "should be considered as trends" rather than absolute values.
• Ct values "should not be used" to define whether or not an individual is infectious.

Abbreviations: COVID-19, coronavirus disease 2019; Ct, cycle threshold; NAAT, nucleic acid amplification test; RNA, ribonucleic acid; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

with an upper limit of 10% if quarantine is ended after 10 days in asymptomatic contacts who are not tested. Testing at the start of quarantine provides no additional benefit and is not recommended.

Testing Asymptomatic Individuals in Settings With High Risk of Transmission

In settings that combine high prevalence, increased transmission risk, and/or higher likelihood of severe disease, a more intensive testing regimen of asymptomatic individuals may be warranted. Examples include densely staffed workplaces, congregate settings, and cohorts with high rates of medical comorbidity (such as manufacturing and agricultural factories, inpatient psychiatric facilities, long-term acute care hospitals, or long-term care facilities). In these settings, the harm of missing a diagnosis includes risk to the individual and the risk of missing an outbreak at its early stages. Along with testing, available engineering controls (eg, adequacy of ventilation in the work environment, filtration efficiency, physical barriers, etc) and administrative controls

(eg, work scheduling, minimizing face-to-face contact, use of masks, etc) are important considerations in these settings.

A reasonable approach when resources permit is for such facilities to follow regional incidence numbers and test positivity rates, with strategies in place allowing initiation of broad test-based screening when a preset threshold (eg, >1% test positivity) is crossed (Table 5). Given the transmission dynamics of SARS-CoV-2, screening would ideally be done no less than twice weekly with results available within 24 hours [22], although this is not always possible. Under significant resource constraints, limiting testing to specific subpopulations may be considered. For example, the Centers for Medicare & Medicaid Services require nursing home staff rather than residents be tested, because staff may be the more likely to introduce the virus into congregate settings, rather than patients with limited outside social activities (https://www.cdc.gov/mmwr/volumes/69/wr/mm695152a3.htm). In situations in which there are ongoing cases, testing of

both staff and residents should be considered. Although NAATs have higher sensitivity, Ag RDTs are less expensive, provide rapid results, and could be particularly useful for frequent testing of asymptomatic staff. The CDC has specifically addressed recommendations for use of antigen testing in nursing homes [23].

Testing Asymptomatic Individuals in K-12 School Settings

Testing students and staff in K-12 school settings for SARS-CoV-2 to support in-person learning has been a challenge throughout the pandemic. Consideration of engineering controls (eg, adequacy of ventilation in the environment, filtration efficiency, physical barriers, etc) and administrative controls (eg, cohorting, minimizing face-to-face contact, etc) must also be part of any in-person learning strategy. Additional considerations must be taken into account for college and university settings, where students are older and transmission risks are differ versus those seen in younger individuals (Supplemental Table 1).

Table 4. Summary of Testing for Individuals Postexposure to COVID-19 Cases

Goals of Testing
Identify COVID-19 cases
Reduce time of quarantine postexposure
Pretest probability: Moderate-high
Testing strategy: Test exposed individual on day 5–7 of quarantine, using Ag RDT or NAAT
Positive result: Quarantine according to local guidance.
Negative result: Quarantine may end on day 7, provided individual remains asymptomatic and acceptable by local guidance.

Abbreviations: Ag, antigen; COVID-19, coronavirus disease 2019; NAAT, nucleic acid amplification test; RDT, rapid diagnostic test.

Table 5. Summary of Testing Considerations for Individuals in Settings With High-Risk of Transmission

Primary Goal of Testing:
    Identify COVID-19 cases.
    Identify transmission early in course of outbreak in a specific population

Pretest Probability: Moderate-low

Testing strategy:
    Screen all individuals at least 1 times per week, using an Ag RDT or NAAT, if local prevalence reaches predefined threshold (eg, 1% test positivity).
    May consider prioritizing testing staff and other individuals in setting that are exposed to the community over facility residents not exposed to community.

Positive result: Rapid quarantine and contact tracing. Institute heightened infection prevention activities if evidence of within-setting transmission.
Negative result: Continue standard infection control activities.

Abbreviations: Ag, antigen; COVID-19, coronavirus disease 2019; NAAT, nucleic acid amplification test; RDT, rapid diagnostic test.

Access to expedited testing for symptomatic individuals is needed. Symptomatic individuals in the K-12 school setting should be tested as described for other symptomatic patients in Table 1, although some special considerations (ie, expedited testing with results available in 24 hours) may be required to meet the goal of continued in-person learning. Some schools have initiated testing using Ag RDTs in school-based health centers [15] for individuals who become sick at school. Confirmatory testing by standard NAAT or rapid RT-PCR is indicated for adults and children with negative Ag RDT results but signs and symptoms consistent with COVID-19. The same expedited diagnostic testing approach used for symptomatic individuals can be applied to testing those with close unmasked contact (within 6 feet for at least 15 minutes) with a confirmed case; close contacts should be quarantined for (1) a minimum of 10 days if no testing is performed or (2) a minimum of 7 days if testing is performed on day 5–7 after

exposure (see above). School policies will depend on local public health policies as well as CDC guidance.

Less consensus exists regarding best practices for screening of asymptomatic staff and students in the K-12 school setting who lack a known exposure (Table 6). Scientific, political, financial, and emotional factors, in addition to community case rates and access and resources for testing, should be considered. Goals of asymptomatic testing programs include collecting data on in-school prevalence for comparison with the surrounding community rates, detection of in-school transmission to inform the effectiveness of infection prevention measures, detection of asymptomatic cases to allow isolation and contact tracing, and overall community reassurance to support in-person learning. It is unfortunate that the high cost and operational complexity of implementing large-scale screening programs in the K-12 setting combined with the lack of coordinated federal or state support to guide specific screening strategies has left each school

and/or district to make its own decisions, with consequent confusion and inequity. Selection of any screening strategy should be based on assessment of school risk level [14], with asymptomatic screening utility rising when the risk of in-school transmission is moderate to high [15]. The CDC guidelines recommend that (1) testing staff should be prioritized over students in any sampling strategy and (2) older students prioritized over younger students.

Choice of test modality for an asymptomatic screening program will depend on testing options available and their relative sensitivity, specificity, turnaround time, operational complexity, and cost. It is challenging to operationalize point-of-care testing of large groups with Ag RDTs.

In light of the shortage of SARS CoV-2 test components and staffing required to perform the testing, pooled testing may be a strategy to meet the needs of testing in schools. Pooled testing involves combining multiple specimens of the same type and testing as 1 specimen (https://www.fda.gov/medical-devices/

Table 6. Summary of Testing Considerations for K-12 School Settings

Primary Goals of Testing:
    • Detect COVID-19 cases.
    • Detect asymptomatic cases to allow isolation and contact tracing and to provide data on the effectiveness of infection prevention measures.
    • Support in-person learning.

Pretest Probability: low

Testing Strategy:
    Develop screening strategy to be implemented if risk of in-school transmission becomes moderate-high. Prioritize testing staff over students and prioritize older students over younger students.
    Testing may be performed every 3 days using Ag RDTs (if supply allows), given their lower sensitivity, or less frequently if traditional NAAT is used.
    In high-volume setting such as K-12 settings, consideration to pooled testing may be of value.

Positive result: Rapid isolation of case and contact tracing. Institute heightened infection prevention activities if evidence of in-school transmission.
Negative result: Continue routine infection prevention activities.

Abbreviations: Ag, antigen; COVID-19, coronavirus disease 2019; NAAT, nucleic acid amplification test; RDT, rapid diagnostic test.

coronavirus-covid-19-and-medical-devices/pooled-sample-testing-and-screening-testing-covid-19). If the pool sample is negative, all specimens within the pool are considered negative. However, if the pool is positive, specimens that constituted the pool are retested individually to determine which led to the positive result. Such testing is associated with logistical and regulatory complexities for the laboratory, and this is only of value if regional positivity rates are low. Programs desiring to implement pooled testing should discuss feasibility with testing laboratories.

Testing Asymptomatic Individuals in Nonhealthcare Essential Workplaces

Nonhealthcare workplaces are an important setting for prevention of SARS-CoV-2 transmission, because these workplaces constitute a major source of job and economic stability for individuals and the country. In the United States, there are more than 160 million employed civilians with an estimated 87 million nonhealthcare essential workers. The CDC has provided guidance for testing strategies in high-density critical infrastructure workplaces after a COVID-19 case is identified [24]. There is wide variability as to which strategy employers have used [25] and how local jurisdictions apply guidance for defining essential workers [26]. The role of workplace testing strategies is less clear in other situations, such as high-density critical infrastructure workplaces without a COVID-19 case, standard-density critical infrastructure workplaces, or workplaces not designated as critical.

Factors that inform the testing approach in a workplace include feasibility of engineering controls (eg, adequacy of ventilation in the work environment, filtration efficiency, physical barriers, etc) and administrative controls (eg, work scheduling, minimizing face-to-face contact, employee travel, etc), situations in which facemasks are not worn (eg, nonadherence, eating or sleeping quarters without sufficient distancing), ability to perform symptom screening upon entry to workplace [27], local/regional prevalence, and epidemic trajectory. During defined periods of moderate to high risk of workplace transmission, along with implementation of established mitigation strategies, it is reasonable to consider serial screening if testing resources are available. When testing is performed, a test with short turnaround time (eg, <24 hours) is preferred, particularly in situations in which critical infrastructure workers continue to work while awaiting test results (Table 7). If workers will be required to quarantine either the full 14 days or until negative test results are received, using a higher sensitivity test with longer turnaround time (PCR) for baseline testing can be considered.

Testing Asymptomatic Travelers

Travel entails contact with individuals outside of one's household, thereby increasing the risk of COVID-19 exposure. Travel via shared vehicles (cars, buses, trains, ships, or airplanes) may pose the greatest risk, because the traveler is put into close contact with large numbers of individuals both in the vehicle

and in potentially crowded departure and arrival terminals, sometimes for long periods of time. Testing might reduce the risk of COVID-19 among travelers and their contacts, if travelers who test positive then delay or forego travel, or if they take extra precautions to prevent onward transmission of SARS-CoV-2. Several states and many international destinations require a negative SARS-CoV-2 diagnostic test result within a prescribed number of days before entry, including the United States for incoming travelers from foreign destinations as of January 26, 2021. Specifically, the CDC requires all air passengers arriving to the United States from a foreign country be tested no more than 3 days before their flight departs and to present the negative test or documentation of having recovered from COVID-19 to the airline before boarding the flight (https://www.cdc.gov/coronavirus/2019-ncov/travelers/testing-international-air-travelers.html). In addition, the CDC recommends testing 3–5 days after travel and self-quarantine for 7 days after travel. Local testing requirements for incoming travelers are subject to frequent modifications, and the most up-to-date guidance should be sought for local juridictions. Proof of a negative test result is often required after arrival at the destination, sometimes regardless of the test result before departure. In some jurisdictions, including the United States, testing is used to reduce the required period of posttravel quarantine from 10 to 7 days (Table 8). It should be noted that a negative test result does not guarantee absence of active or incubating

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Table 7. Summary of Testing Considerations for Nonhealthcare Essential Workplaces

Primary Goals of Testing:
Identify COVID-19 cases.
Maintain essential services, reduce transmission in workplace.
Pretest probability: Low-moderate
Testing Strategy:
Perform a test with short turnaround time (eg, <24 hours), particularly in situations where critical infrastructure workers are continuing to work while awaiting test results. Frequency of screening will depend on type of test used, time to results, local prevalence, and work environment.
Positive result: Rapid quarantine and contact tracing. Institute heightened infection prevention activities if evidence of within-workplace transmission.
Negative result: Continue with standard infection prevention protocols.

Abbreviations: COVID-19, coronavirus disease 2019.

Table 8. Summary of Testing Considerations for Asymptomatic Travelers

Primary goals of testing: Reduce risk of SARS-CoV-2 transmission during travel and at destination; reduce period of quarantine after arrival at destination; a negative test result may be required for entry to a country or locality.

Pretest probability of infection: Low–moderate

Testing strategy:
- Test within 1–3 days of departure.
- May test upon arrival, then 3–5 days after arrival AND quarantine for 7 days at destination, even if test negative.
- If no testing upon arrival, quarantine for 10 days.

Positive result: If test positive before departure, delay travel and self-isolate. If test positive at destination, self-isolate until local criteria for release from isolation are met.

Negative result: If test negative before departure, follow standard infection prevention measures (eg, masking, physical distancing). If test negative after arrival, quarantine for period specified by destination rules (ie, 7 days) and follow standard infection prevention measures (eg, masking, physical distancing).

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

infection, and that travelers should continue to mask and avoid close contact in crowded locations before and after travel. The type of test performed (NAAT or Ag RDT) is not well defined, but detection of presymptomatic infections is best with NAAT testing. Antibody testing may also be required by some locations; IDSA guidance is available to aid with use and interpretation of SARS-CoV-2 antibody tests [28].

Few reports of the value of travel-related testing to reduce the risk of COVID-19 have been published. One simulated model of international travel predicted that screening incoming travelers on arrival and again on day 7 of quarantine would lead to an 88.2% average reduction in secondary COVID-19 cases. The reduction increased to 92.1% if a 14-day quarantine was applied. In contrast, universal quarantine of all travelers upon arrival with no testing was associated with either a 30% (7-day quarantine) or 84.3% (14-day quarantine) reduction in secondary cases [29]. A genomic epidemiologic investigation of an outbreak of COVID-19 associated with an 18-hour airplane flight showed that in-flight transmission of SARS-CoV-2 can occur despite predeparture testing [30]. In this study, 2 travelers were found to be index cases for 4 in-flight transmissions, despite testing negative for SARS-CoV-2 by PCR approximately 4 days before boarding. Mask use was not mandatory on this flight, but several of the cases self-reported mask and glove use while on the airplane.

One additional important consideration when testing travelers is the emergence of global SARS-CoV-2 variants with mutations in genes targeted by diagnostic tests, which may impact the test's sensitivity. For example, the SARS-CoV VOC202012/01 or B.1.1.7 variant harbors several mutations in the spike protein. This variant can result in "S gene dropout" leading to reduced analytical sensitivity for assays that target the spike gene, including deletion at positions 69–70. Most commercial assays target more than 1 viral gene, which minimizes the chances of a false-negative result but increases the likelihood of an indeterminate result if not all viral targets are detected on a given assay. If travelers or contacts of travelers from regions with widespread transmission of SARS-CoV-2 variants present with negative tests but a high clinical suspicion for infection (ie, symptoms consistent with COVID-19), review of the genetic targets of the assay used is prudent, with potential confirmatory testing by an alternative method. This is also true for patients without travel, if domestic circulation of these strains is suspected or known. Descriptions of the tests known to be impacted by the 69–70 mutation are available from the FDA (https://www.fda.gov/medical-devices/letters-health-care-providers/genetic-variants-sars-cov-2-may-lead-false-negative-results-molecular-tests-detection-sars-cov-2). Due to widespread circulation of SARS-CoV-2, more variants are anticipated, which may impact the performance of current tests;

laboratories should routinely monitor the performance of their tests, and clinicians should communicate with the laboratory if false-negative results are suspected. In addition, the FDA requires manufacturers to report any suspected occurrence of flase-positive and false-negative results and significant deviations from the established performance characteristics of the COVID-19 diagnostic product of which they become aware.

Home Self-Testing Using Point-of-Care Rapid Antigen Tests

Although at-home specimen collection kits have been available since early in the pandemic, the FDA EUA has only recently been granted for 3 home-based testing kits (2 Ag RDTs and 1 NAAT assay), 2 of which require a prescription. One Ag RDT is read visually and the other by a smartphone interface. The NAAT test uses a disposable module with Smartphone interpretations and reporting of results. There is limited experience with these assays and no published clinical studies that evaluate these tests in a home-testing strategy. Of note, the financial burden of such testing may be left to the patient, precluding use of these tests in areas of lower economic means, often affecting populations disproportionately impacted by COVID-19.

Per manufacturer-performed studies on a limited number of individuals, both tests performed well, demonstrating good agreement with reference method NAAT. Agreement was best for symptomatic individuals tested within 7 days

Table 9. Summary of Considerations for the Use of Home Testing Using Rapid Antigen Tests

Primary Goals of Testing:
Identification of asymptomatic COVID-19 infections, enable more convenient testing of symptomatic individuals
Pretest probability: low (asymptomatic), high (symptomatic)
Testing strategy: None defined to date
Positive result: Consider confirmation by NAAT
Negative result: Confirmation by NAAT, if symptomatic

Abbreviations: COVID-19, coronavirus disease 2019; NAAT, nucleic acid amplification test.

of symptom onset, followed by asymptomatic individuals, and finally patients with >7 days of symptoms (https://www.fda.gov/media/144457/download; https://www.fda.gov/media/144574/download).

It is notable that 1 test was evaluated in a population with a high positivity rate (20%, including 8% in asymptomatic patients). Testing in the context of lower prevalence rates will significantly change the PPV and NPV of these tests.

Home self-testing is dependent on the ability of the operators to (1) follow instructions accurately, (3) ensure that test kits are not expired, and (3) understand the limitations of both negative and positive results depending on the clinical scenario. The decision to implement home-based Ag RDT in any type of large-scale screening or diagnostic program will require close monitoring, and the success of this may be very dependent upon the community prevalence of disease—for example, very low community prevalence rates will result in increased rates of false-positive results, due to a low pretest probability. Until improved knowledge of the performance and use of these tests is available, individuals performing self-testing at home should be tested by NAAT if they have symptoms consistent with COVID-19 but obtain a negative home Ag RDT. Similarly, positive cases by Ag RDT should be confirmed to ensure specificity (particularly if local prevalence rates are low), appropriate public health tracking, and linkage to care (Table 9).

Testing Asymptomatic Contacts of Contacts
There is no current evidence to support testing secondary contacts of individuals exposed to COVID-19-infected individuals. If a primary contact should develop symptoms and/or be diagnosed with COVID-19, the contacts of that individual can benefit from testing, because they would then be direct primary contacts.

CONCLUSIONS

The use of tests to detect the presence of SARS-CoV-2 Ag or RNA among individuals, including those without symptoms of COVID-19, can provide significant benefit when used in the context of comprehensive infection prevention programs, during this pandemic. Any strategy that incorporates testing must consider several factors, including the risks of testing (ie, impact of false-positive and false-negative results), the pretest probability of the population tested and how that impacts interpretation of test results, how the results will be incorporated into management strategies, the location of testing, and the types of tests applied. Over the past year, an immense effort to develop, authorize, and distribute tests for SARS-CoV-2 has been made. Despite this, significant testing challenges remain, including limited availability of test components, ancillary supplies (eg, swabs or pipette tips), and testing personnel. As such, testing strategies must also give serious consideration to (1) feasibility of the approach and (2) prioritization of testing symptomatic individuals above those who are asymptomatic. As the pandemic progresses, it is probable that the dynamics surrounding the scenarios described herein will change—notably, as disease rates change and vaccination efforts progress. Nonetheless, the guiding principle of using testing as an important component of a comprehensive management program remains.

References

1. Centers for Disease Control and Prevention. Interim guidelines for COVID-19 antibody testing in clinical and public health settings. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html. Accessed 12 February 2021.
2. IDSA. Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: serological testing. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-serology/. Accessed 12 February 2021.
3. Hanson KE, Caliendo AM, Arias CA, et al. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Molecular

Diagnostic Testing. Available at: www.idsociety.org/covid19guidelines/dx. Accessed 12 February 2021.

4. Young S, Taylor SN, Cammarata CL, et al. Clinical evaluation of BD Veritor SARS-CoV-2 point-of-care test performance compared to PCR-based testing and versus the Sofia 2 SARS antigen point-of-care test. J Clin Microbiol **2020**; 59:e02338–20.

5. Pray IW, Ford L, Cole D, et al; CDC COVID-19 Surge Laboratory Group. Performance of an antigen-based test for asymptomatic and symptomatic SARS-CoV-2 testing at two university campuses - Wisconsin, September-October 2020. MMWR Morb Mortal Wkly Rep **2021**; 69:1642–7.

6. Pilarowski G, Lebel P, Sunshine S, et al. Performance characteristics of a rapid SARS-CoV-2 antigen detection assay at a public plaza testing site in San Francisco. J Infect Dis **2021**. In press.

7. Pollock NR, Tran K, Cranton A, et al. Performance and implementation evaluation of the Abbott BinaxNOW rapid antigen test in a high-throughput drive-through community testing site in Massachusetts. J Clin Microbiol **2021**. In press.

8. Kociolek LK, Muller WJ, Yee R, et al. Comparison of upper respiratory viral load distributions in asymptomatic and symptomatic children diagnosed with SARS-CoV-2 infection in pediatric hospital testing programs. J Clin Microbiol **2020**; 59:e02593–20.

9. Centers for Disease Control and Prevention. Interim guidance for antigen testing for SARS-CoV-2. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html. Accessed 12 February 2021.

10. Cevik M, Tate M, Lloyd O, et al. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe **2021**; 2:e13–22.

11. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis **2020**; 20:565–74.

12. Singanayagam A, Patel M, Charlett A, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill **2020**; 25:2001483.

13. Choi B, Choudhary MC, Regan J, et al. Persistence and evolution of SARS-CoV-2 in an immunocompromised host. N Engl J Med **2020**; 383:2291–3.

14. Rivers C, S C, Potter, C, et al. Risk assessment and testing protocols for reducing SARS-CoV-2 transmission in K-12 schools. Available at: https://www.rockefellerfoundation.org/wp-content/uploads/2020/10/Risk-Assessment-and-Testing-Protocols-for-Reducing-SARS-CoV-2-Transmission-in-K-12-Schools_Final-10-14-2020.pdf. Accessed 12 February 2021.

15. Centers for Disease Control and Prevention. Interim Considerations for Testing for K-12 School Administrators and Public Health Officials. Dec. 4, **2020**. Available at: https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/k-12-testing.html.

16. American Society for Microbiology. Supply shortages impacting COVID-19 and non-COVID testing. Available at: https://asm.org/Articles/2020/September/Clinical-Microbiology-Supply-Shortage-Collecti-1. Accessed 12 February 2021.

17. Centers for Disease Control and Prevention. Interim U.S. guidance for risk assessment and work restrictions for healthcare personnel with potential exposure to COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html. Accessed 12 February 2021.

18. Centers for Disease Control and Prevention. Public health guidance for community-related exposures. Available at: https://www.cdc.gov/coronavirus/2019-ncov/php/public-health-recommendations.html. Accessed 12 February 2021.

19. Guan WJ, Ni ZY, Hu Y, et al.; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med **2020**; 382:1708–20.

20. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med **2020**; 382:1199–207.

21. Centers for Disease Control and Prevention. Options to reduce quarantine for contacts of persons with SARS-CoV-2 infection using symptom monitoring and diagnostics testing. Available at: https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-options-to-reduce-quarantine.html. Accessed 12 February 2021.

22. Paltiel AD, Zheng A, Walensky RP. Assessment of SARS-CoV-2 screening strategies to permit the safe reopening of college campuses in the United States. JAMA Netw Open **2020**; 3:e2016818.

23. Centers for Disease Control and Prevention. Considerations for use of SARS-CoV-2 antigen testing in nursing homes. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/nursing-homes-antigen-testing.html. Accessed 12 February 2021.

24. Centers for Disease Control and Prevention. Testing Strategy for Coronavirus (COVID-19) in High-Density Critical Infrastructure Workplaces after a COVID-19 Case Is Identified. Available at: https://www.cdc.gov/coronavirus/2019-ncov/community/worker-safety-support/hd-testing.html. Accessed 16 December 2020.

25. Waltenburg MA, Victoroff T, Rose CE, et al; COVID-19 Response Team. Update: COVID-19 among workers in meat and poultry processing facilities - United States, April-May 2020. MMWR Morb Mortal Wkly Rep **2020**; 69: 887–92.

26. US Departent of Homeland Security CISA. Guidance on the essential critical infrastructure worforce: ensuring community and national resilience in COVID19 response (V 4.0). **2020**.

27. U.S. Department of Labor. Coronavirus: guidance on preparing workplaces for COVID-19. **2020**. Available at: https://www.osha.gov/sites/default/files/publications/OSHA3990.pdf. Accessed 12 February 2021.

28. Hanson KE, Caliendo AM, Arias CA, et al. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: serologic testing. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa1343

29. Dickens BL, Koo JR, LIm JT, et al. Strategies at points of entry to reduce importation risk of COVID-19 cases and reopen travel. J Travel Med **2020**; 27:taaa141.

30. Swadi T, Geoghegan JL, Devine T, et al. Genomic evidence of in-flight transmission of SARS-CoV-2 despite predeparture testing. Emerg Infect Dis **2021**; 27:687–93.