The Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Antigen Testing

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Abstract

Background: Immunoassays designed to detect SARS-CoV-2 protein antigens are now commercially available. The most widely used tests are rapid lateral flow assays that generate results in approximately 15 minutes for diagnosis at the point-of-care. Higher throughput, laboratory-based SARS-CoV-2 antigen (Ag) assays have also been developed. The overall accuracy of SARS-CoV-2 Ag tests, however, is not well defined. The Infectious Diseases Society of America (IDSA) convened an expert panel to perform a systematic review of the literature and develop best practice guidance related to SARS-CoV-2 Ag testing. This guideline is the third in a series of rapid, frequently updated COVID-19 diagnostic guidelines developed by IDSA.

Objective: IDSA's goal was to develop evidence-based recommendations or suggestions that assist clinicians, clinical laboratories, patients, public health authorities, administrators and policymakers in decisions related to the optimal use of SARS-CoV-2 Ag tests in both medical and non-medical settings.

Methods: A multidisciplinary panel of infectious diseases clinicians, clinical microbiologists and experts in systematic literature review identified and prioritized clinical questions related to the use of SARS-CoV-2 Ag tests. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the certainty of evidence and make testing recommendations.

Results: The panel agreed on five diagnostic recommendations. These recommendations address antigen testing in symptomatic and asymptomatic individuals as well as assess single *versus* repeat testing strategies.

Conclusions: Data on the clinical performance of U.S. Food and Drug Administration SARS-CoV-2 Ag tests with Emergency Use Authorization is mostly limited to single, one-time testing *versus* standard nucleic acid amplification testing (NAAT) as the reference standard. Rapid Ag tests have high specificity and low to modest sensitivity compared to reference NAAT methods.

Antigen test sensitivity is heavily dependent on viral load, with differences observed between symptomatic compared to asymptomatic individuals and the time of testing post onset of symptoms. Based on these observations, rapid RT-PCR or laboratory-based NAAT remain the diagnostic methods of choice for diagnosing SARS-CoV-2 infection. However, when molecular testing is not readily available or is logistically infeasible, Ag testing can help identify some individuals with SARS-CoV-2 infection. The overall quality of available evidence supporting use of Ag testing was graded as very low to moderate.

Executive Summary

Diagnostic testing remains an important tool to combat the ongoing SARS-CoV-2 pandemic. SARS-CoV-2 antigen (Ag) tests are now widely available, which has helped to expand testing capacity to settings outside of the hospital or clinic. Most SARS-CoV-2 Ag tests in clinical use are point-of-care (POC) lateral flow devices that generate results in approximately 15 minutes. Laboratory-based Ag test platforms also exist, but experience with their performance and utility is more limited. The main advantage of POC testing is the availability of results during an encounter, which facilitates immediate communication on the need for isolation and/or contact tracing, as well as informs potential treatment decisions. Antigen tests, however, are generally less sensitive than standard molecular diagnostic methods (i.e., rapid RT-PCR and laboratory-based nucleic acid amplification testing [NAAT]). Given the recent expansion of the diagnostic literature along with increasing test availability, IDSA recognized the need for evidence-based guidelines related to the use of U.S. Food and Drug Administration (FDA) Emergency Use Authorization (EUA) SARS-CoV-2 Ag tests.

The overall specificity of SARS-CoV-2 Ag testing was ≥ 99% compared to standard NAAT (i.e., rapid RT-PCR or laboratory-based NAAT; **Figure s2b**). Therefore, routine confirmation of positive Ag results by a reference molecular method does not appear to be necessary, even in most low prevalence settings. Alternatively, Ag test sensitivity varied widely across studies and was dependent on the presence or absence of documented COVID-19 symptoms and the time of testing after symptom onset. Pooled Ag test sensitivity was 84% for symptomatic individuals tested within the first seven days of illness (**Figure s9a**), 62% after seven days or more of

symptoms (**Figure s12a**) and 49% (**Figure s15a**) for those without symptoms. Antigen tests performed similarly in adults and children (**Figures s3a-s4b**).

Specific recommendations and comments related to the use of SARS-CoV-2 Ag tests with FDA-EUA status are summarized below. A detailed description of background, methods, evidence summary, and rationales that support each recommendation, as well as unmet research needs can be found online in the full text. Briefly, an expert panel consisting of clinicians, medical microbiologists and methodologists critically appraised the SARS-CoV-2 Ag diagnostic literature using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the certainty of evidence. Per GRADE, recommendations are categorized as "strong" or "conditional". The word "recommend" indicates a strong recommendation and "suggest" indicates a conditional recommendation. This guideline assumed availability of rapid Ag testing and focuses on testing for diagnosis and asymptomatic screening.

Given the superior sensitivity of molecular diagnostics, the panel suggests the use of standard NAAT over Ag tests, especially for individuals with symptoms of COVID-19 or when the implications of missing the diagnosis of SARS-CoV-2 are significant (such as for hospitalized patients, in long-term care facilities, or when screening for asymptomatic infection before major surgery). For symptomatic patients, if Ag testing is used, negative results should be confirmed by standard NAAT when the clinical suspicion of COVID-19 is high. Ultimately, deciding whether to use rapid Ag tests in lower-risk, non-medical settings will depend on a number of factors including the prevalence of disease in the population combined with an assessment of the value of detecting true SARS-CoV-2 infection *versus* the detrimental effects of erroneous results (i.e., false negative and false positive results). The feasibility of test implementation and costs of testing are also important considerations.

Recommendation 1: For symptomatic individuals suspected of having COVID-19, the IDSA panel suggests using standard NAAT (either rapid RT-PCR or laboratory-based NAAT) over rapid Ag tests (*conditional recommendation based on moderate certainty in test accuracy of rapid Ag test and very low certainty in comparative test accuracy of rapid RT-PCR* versus *rapid Ag tests*)

Remarks:

- Symptomatic individuals were defined as those with at least one of the common symptoms of COVID-19 (**Table 1, IDSA Guidelines on the Diagnosis of COVID-19: Molecular Diagnostic Testing**).
- If NAAT is not available or results are expected to be delayed beyond 2 – 3 days, rapid Ag testing could be considered.
- For optimal performance, Ag tests should be used within seven days of symptom onset.
- If clinical suspicion for COVID-19 remains high, negative Ag results should be confirmed by standard NAAT.
- Infectiousness of an individual cannot be determined based on Ag testing or NAAT results.

Recommendation 2: For asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests using a single standard NAAT (either rapid RT-PCR or laboratory-based NAAT) over a single rapid Ag test (*conditional recommendation based on moderate certainty in test accuracy of rapid Ag tests and very low certainty in comparative test accuracy of rapid RT-PCR* versus *rapid Ag tests*)

Remarks:

- SARS-CoV-2 testing in the absence of COVID-like symptoms should be individualized. Vaccination status and history of prior laboratory-confirmed SARS-CoV-2 infection may affect decisions about whether or not to test in certain situations.
- One-time screening at the time of inpatient or long-term care facility admission, or before major surgery, should be done using a rapid RT-PCR or a laboratory-based NAAT. Standard NAATs are desirable for such populations because the higher sensitivity of these methods reduces the likelihood of missing individuals with SARS-CoV-2 infection who could inadvertently expose other vulnerable

patients or healthcare personnel. In addition, perioperative SARS-CoV-2 infection may increase risk for pulmonary complications and mortality. Testing can help inform surgical planning.

- One-time screening in community settings (e.g., schools, workplaces, airports) should also ideally be performed using standard NAATs when the pre-test probability is moderate to high (i.e., ≥ 5%). When standard NAAT is not available, rapid Ag testing could be considered.
- One-time testing using NAAT or Ag can be considered in cases of known close contact when the individual cannot be effectively or safely quarantined for 10-14 days. Per current Centers for Disease Control and Prevention (CDC) guidance, testing on day 5-7 post-exposure can help inform discontinuation of quarantine as early as day seven [1].

Recommendation 3: For asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests a single (i.e., one-time) standard NAAT (either rapid RT-PCR or laboratory-based NAAT) rather than a strategy of two consecutive rapid Ag tests (*conditional recommendation based on moderate certainty in test accuracy of molecular testing and an evidence gap to inform the test accuracy of a strategies using repeat Ag testing*)

Remarks:

- SARS-CoV-2 testing in the absence of COVID-like symptoms should be individualized. Vaccination status and history of prior laboratory-confirmed SARS-CoV-2 infection may affect decisions about whether or not to test in certain situations.
- One-time screening at the time of inpatient or long-term care facility admission or before major surgery should be done using a single rapid RT-PCR or a single laboratory-based NAAT. Standard NAATs are desirable for such populations because the higher sensitivity of these methods reduces the likelihood of missing

individuals with SARS-CoV-2 infection that could inadvertently expose other vulnerable patients or healthcare personnel. In addition, perioperative SARS-CoV-2 infection may increase risk for pulmonary complications and mortality. Testing can help inform surgical planning.

- One-time screening in community settings (e.g., schools, workplaces, airports) should also ideally be performed using a single standard NAATs when the pre-test probability is moderate to high (i.e., ≥ 5%). If standard NAATs are not available, performance of a rapid Ag test followed by a second rapid Ag test if the first is negative (i.e., two consecutive tests) could be considered.
- If two rapid Ag tests are performed, sequential testing during the same clinical encounter, when the first test is negative, does not appear to improve sensitivity. The optimal timing between two sequential tests has not been established.
- The strategy of performing two sequential Ag tests only may not apply to facilities experiencing an ongoing outbreak.

Recommendation 4: In asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests neither for nor against using single (i.e., one-time) rapid Ag testing over no testing (evidence gap to inform the utility of Ag testing compared to no testing)

Remarks:

- SARS-CoV-2 testing in the absence of COVID-like symptoms should be individualized. Vaccination status and history of prior laboratory-confirmed SARS-CoV-2 infection may affect decisions about whether or not to test in certain situations.
- One-time Ag testing (*versus* no testing) can be considered in cases of known close contact when the individual cannot be effectively or safely quarantined for 10-14 days. Per current CDC guidance, testing on day 5-7 post-exposure can help inform discontinuation of quarantine as early as day seven [1].

- One-time Ag testing (*versus* no testing) immediately before an event or travel may be useful for reducing transmission particularly when distancing is not possible, or the ventilation is poor, and community prevalence is moderate to high i.e., (≥ 5%). In these scenarios, someone who tested positive would be excluded from the event/travel and require isolation, while those who tested negative would still need to adhere to prevention measures such as masking during the event or flight.

Recommendation 5: In asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests neither for nor against using repeat rapid Ag testing over no testing (*evidence gap to inform the utility of a strategy of Ag testing compared to no testing)*.

Remarks:

- SARS-CoV-2 testing in the absence of COVID-like symptoms should be individualized. Vaccination status and history of prior laboratory-confirmed SARS-CoV-2 infection may affect decisions about whether or not to test in certain situations.
- Repeat Ag testing (*versus* no testing) is likely to have utility in congregate settings experiencing an outbreak.
- Repeat Ag testing (*versus* no testing) is also expected to detect some asymptomatic infections in populations with moderate to high prevalence (i.e., ≥5%)
- If repeated Ag tests are performed, the optimal number, timing and duration of testing has not been established and may vary by the indication for testing.

Background

Making a rapid and accurate diagnosis of SARS-CoV-2 infection remains an essential component of comprehensive mitigation strategies aimed at curtailing the COVID-19 pandemic. Standard NAAT, defined throughout this document as rapid RT-PCR and laboratory-based NAATs, is considered the reference method for diagnosing COVID-19 as well as for identifying cases of asymptomatic infection. However, over the course of the pandemic, especially early on, molecular diagnostic test shortages and delayed test turnaround times plagued testing initiatives in many locations.

Antigen tests that detect SARS-CoV-2 proteins are now commercially available, which has helped to address the ongoing need for widespread access to SARS-CoV-2 testing. While Ag-based assays for respiratory viruses are generally less sensitive than reference molecular methods, Ag tests can be easier and faster to perform and these assays are typically less expensive than NAAT. In addition, rapid Ag testing can be deployed outside of clinic or hospital settings, with analysis performed by non-medical staff. **Table 1** compares the advantages and limitations of Ag testing *versus* NAAT.

Table 1. Comparisons between Antigen and Molecular Diagnostic Tests

Test features	Antigen tests	Nucleic acid amplification tests
Methods	• Rapid LFAs [a] read either manually or with a reader • Laboratory-based immunoassays of various types	• Rapid RT-PCR • Laboratory-based NAAT (e.g., RT-PCR, TMA) • Rapid isothermal NAAT
Targets	Viral protein • Most detect nucleocapsid protein	Viral RNA • Various gene targets encoding structural and/or non-structural proteins
Specimen types [b]	• Anterior nasal, mid-turbinate, or nasopharyngeal swabs	• Anterior nasal, mid-turbinate, nasopharyngeal and/or oropharyngeal swabs • Saliva, sputum or bronchoalveolar lavage fluid
Point-of-care use	• Rapid LFA tests (3 manufacturers have tests authorized for home testing)	• Include some rapid isothermal NAATs and rapid-RT PCR tests (2 authorized for home testing)
Advantages	• LFAs have short turnaround times, with results available during the encounter (~15 minutes) • LFAs have comparable performance to some isothermal NAATs for symptomatic patients and/or when culturable virus is present in the sample • Generally less expensive than NAAT • Most assays target nucleocapsid proteins, which may be less affected by virus evolution (mutations)	• Standard [c] NAAT is the most sensitive method available (i.e., least false negatives) and therefore does not require repeated testing to confirm results • Isothermal NAATs and rapid RT-PCRs have short turn-around-times, with results potentially available during the encounter (~15 – 60 minutes) • Laboratory-based NAATs are amendable to automation and high-throughput testing

Limitations	• Less sensitive (more false negatives) than standard* NAAT, especially for asymptomatic individuals or when testing is performed late in the course of infection • Negative Ag results in symptomatic persons require confirmation with NAAT • Large scale testing using LFAs may be more complicated to scale up than high-throughput laboratory-based NAAT	• Laboratory based NAAT may have long turnaround times, depending on the laboratory • Prolonged RNA shedding is detectable by sensitive NAATs during the recovery phase of COVID-19, which is potentially beyond the presumed period of infectiousness • The sensitivity of molecular assays targeting the spike gene may be affected by circulating variants (gene mutations) • NAAT is generally more expensive than Ag testing

Ag: Antigen; **LFA:** Lateral flow assay; **RT-PCR**: Reverse transcriptase polymerase chain reaction; **NAAT:** Nucleic acid amplification test; **TMA:** Transcription-mediated amplification

Explanations

a. Lateral flow assays also include tests designated as chromatographic digital immunoassays.
b. Approved specimen types vary by test. Alternate types require laboratory validation.
c. Standard NAAT includes rapid RT-PCR and laboratory-based assays.

As of April 2021, 23 SARS-CoV-2 Ag tests have received EUA from the FDA [2]. SARS-CoV-2 Ag tests use monoclonal antibodies to capture and detect viral proteins in respiratory secretions obtained with a nasopharyngeal, mid-turbinate or nasal swab. Depending on the manufacturer, Ag test swabs may either be analyzed directly or placed in an approved transport media or other fluid for testing. Currently available SARS-CoV-2 Ag tests come in a variety of formats including rapid LFAs and other types of immunoassays. Lateral flow assays are the most commonly used method for SARS-CoV-2 Ag detection and are amendable to testing at the POC. In addition, several SARS-CoV-2 LFAs have received EUA designation for home testing. Lateral flow assays are configured as single use test strips with results read either visually or by an instrument in ~15 minutes. Other immunoassay designs may require instrumentation or

procedural steps that must be performed in clinical laboratory by laboratory-trained staff, with results typically generated in under an hour of instrument run time.

All SARS-CoV-2 Ag tests with EUA status are labeled for testing symptomatic individuals suspected having COVID-19. Specifically, most of these assays have indications for use within the first 5, 7, 12, or 14 days of symptom onset depending on the test. Device manufacturers and the CDC recommend confirming negative Ag results with a follow-up reference molecular diagnostic test for symptomatic patients [3]. Antigen testing is also being used for post-exposure testing and for screening purposes (i.e., testing asymptomatic individuals with no known or suspected exposure to a confirmed case of SARS-CoV-2 infection). The Centers for Medicare & Medicaid Services exercised enforcement discretion to allow use of Ag tests in asymptomatic individuals for the duration of the COVID-19 public health emergency. Depending on the indication for testing, Ag testing may also be completed once (single test) or performed sequentially over time (repeated tests).

There is a significant need to understand how EUA Ag tests perform clinically to inform testing strategies for individuals with varying risk for SARS-CoV-2 exposure and disease. IDSA convened an expert panel to systematically review the SARS-CoV-2 Ag diagnostic test literature with a focus on assays with EUA status assays. The panel compared pooled estimates of test accuracy to make evidence-based recommendations for best use in clinical practice. This guide assumes ongoing transmission of SARS-CoV-2 in the community and the availability of EUA designated Ag tests but does not address use for public health surveillance.

Methods

Panel Composition

The panel was composed of clinicians and clinical microbiologists who are members of IDSA, the American Society for Microbiology (ASM), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS). They represent the disciplines of infectious diseases, pediatrics, and medical microbiology. The Evidence

Foundation provided technical support and guideline methodologists for development of this guideline.

Disclosure and Management of Potential Conflicts of Interest

The conflict of interest (COI) review group included two representatives from IDSA who were responsible for reviewing, evaluating, and approving all disclosures. All members of the expert panel complied with the COI process for reviewing and managing COIs, which required disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict, regardless of relevancy to the guideline topic. The assessment of disclosed relationships for possible COIs was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The COI review group ensured that the majority of the panel and chair was without potentially relevant conflicts (i.e., those related to the topic). The chair and all members of the technical team were determined to be unconflicted.

Question Generation

Clinical questions related to the use of SARS-CoV-2 Ag tests were developed into a PICO format (Population, Intervention, Comparison, Outcomes) prior to the first panel meeting (**Table s1**). Panel members prioritized questions with available evidence that met the minimum acceptable criteria (i.e., the body of evidence reported on at least a case-series design; case reports were excluded)

Search Strategy

A comprehensive search of several databases from January 2019 to February 22, 2021 limited to humans and English language was conducted. The databases included PubMed MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and medRxiv. The search

strategy was designed and conducted by an experienced librarian with input from the methodology panel. Controlled vocabulary was used, supplemented with keywords to search for SARS-CoV-2, diagnosis, and Ag testing. Reference lists and literature suggested by panelists were reviewed for inclusion. Preprints were followed for final publication. During the evidence assessment and recommendation process, horizon scans were performed to locate any additional grey literature, manuscript preprints, and literature published after the last search date.

Screening and Study Selection

Four reviewers (AA, OA, RM, PP) independently screened titles and abstracts, and eligible full text studies. We included studies reporting on the diagnostic test accuracy of Ag testing (cohort studies, cross sectional studies and case-control studies). We aimed to identify studies that compared the diagnostic performance of Ag testing or Ag test-based strategies to rapid RT-PCR testing or no testing using a third reference standard. When such studies were not identified, we selected studies that reported diagnostic test accuracy of Ag testing compared to rapid RT-PCR as a reference standard. We limited our inclusion to tests that had FDA EUA as of March 1, 2021. We only included studies that used a single or multiple NAATs as reference standards. We included any study regardless of the prevalence. We included studies regardless of timing of symptom onset as long as they compared antigen testing to the predefined reference standards. We only included studies that used upper respiratory tract samples (anterior nasal, mid-turbinate, or nasopharyngeal swabs). Reviewers extracted relevant information into a standardized data extraction form. Studies of testing strategies were included if they reported the effect of the testing strategy on disease prevalence or outcomes. We did not include studies that compared Ag to viral culture as a reference standard, but the data was collected when presented in any study that met the inclusion criteria. We excluded studies that included fewer than 10 patients for sensitivity or specificity assessment, studies of serologic tests, studies of laboratory-developed tests, tests with no FDA-EUA and studies that did not provide enough information to allow calculation of sensitivity and specificity.

Data Collection and Analysis

Data extraction was performed for each study independently and in duplicate by a member from the methodology team and one clinical expert. Disagreements were resolved by discussion to reach consensus between a methodologist and a clinical expert. The extracted data included general study characteristics (authors, publication year, country, study design), the diagnostic index test and reference standard, prevalence of COVID-19, and parameters to determine test accuracy (i.e., sensitivity and specificity of the index test). For each test, we extracted sampling sites, sampling method (healthcare worker, self, or supervised self-collection), use of transport media (*versus* dry swabs or direct testing), location of sample collection (e.g., ambulatory, hospital-based, field), the target Ag, the test platform (e.g., lateral flow), and the result assessment method (visual *versus* instrument based). We also recorded whether the same specimen was used for Ag and NAAT testing; whether the same site was used for both tests (when different specimens were used); whether the specimen for one test was obtained before the other systematically (e.g., Ag swabs always collected first); whether there was a time gap between collection of specimens (e.g., specimen for NAAT collected on admission followed by specimen for Ag testing collected few days later); and whether the sample was collected from right, left, or both sides when laterality is possible (e.g., nasal swabs), alongside the timing of specimen collection relative to symptom onset.

Accuracy estimates from individual studies were pooled quantitatively using the logit transformation and the bivariate random effects model when there were enough studies. The bivariate model was preferred as it accounts for between study variation as well as correlation between sensitivity and specificity. We used a random effects generalized linear mixed model to pool sensitivity and specificity separately when it was not possible to conduct a bivariate model, and as a sensitivity analysis when the bivariate model was conducted. The Freeman-Tukey double arcsine transformation was used when there were no false negatives or false positives [4, 5]. Heterogeneity between studies was assessed by examining the Forest plots. When the analysis included studies that used different sample types and/or transport media for the index and reference tests, we conducted sensitivity analyses that excluded those studies to

assess robustness of findings. Analyses were performed using the packages mada 0.5.10 and meta 4.11.0 in R 3.6.3 [6-8].

As we did not identify any study that directly evaluated the effect of repeated testing strategies compared to no testing, we conducted simple modeling to simulate sequential testing. An example of the algorithm is provided in **Figure s18a**. Modeling was done by reapplying the sensitivity and specificity to the individuals who test negative after initial testing (both false and true negative), assuming an equal sensitivity and specificity on the first and repeat testing, fixed prevalence and without adjusting for potential variables between the two tests. To calculate absolute differences in effects for different testing or sampling strategies, we applied results of sensitivity and specificity to a range of plausible prevalence in the population. We then calculated true positives, true negatives, false positives, and false negatives.

This guideline assumes risk for acquiring SARS-CoV-2 as a result of exposure in a community, household or facility. To determine the prevalence of infection for each PICO question, we considered the published literature in consultation with the clinical experts. Prevalence, as defined by the results of surveillance NAAT testing over the last 14 days in each community, has been shown to change over time. For purposes of the guideline, we applied 1%, 5%, and 10% pre-test probability to mirror a range of community prevalence and used 20% to 30% pre-test probability for cases of known close contact or during outbreaks. Instances of higher pre-test probability include symptomatic patients, residence in a community with high prevalence and/or a person living in a household or with continued contact to someone with confirmed COVID-19 within the antecedent 14 days. For comparative purposes, the diagnostic accuracy of rapid RT-PCR and laboratory-based NAAT were calculated *versus* a composite reference standard that combined the results of multiple NAATs (Table 3, **Table s4**, and **Table s5**).

Risk of Bias and Certainty of Evidence

We conducted the risk of bias assessment for diagnostic test accuracy studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 revised tool (**Tables s2a-s2c**)

[9]. GRADE framework was used to assess overall certainty by evaluating the evidence for each outcome on the following domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias [10, 11]. GRADE summary of findings tables was developed in GRADEpro Guideline Development Tool [12].

Evidence to Recommendations

The panel considered core elements of GRADE evidence in the decision process, including certainty of evidence and balance between desirable and undesirable effects. Additional domains were acknowledged where applicable (e.g., feasibility, resource use, acceptability). For all recommendations, the expert panelists reached consensus. Voting rules were agreed on prior to panel meetings for situations when consensus could not be reached.

As per GRADE methodology, recommendations are labeled as "strong" or "conditional". The words "we recommend" indicate strong recommendations, with "we suggest" indicating conditional recommendations. **Figure 1** provides the suggested interpretation of strong and weak recommendations for patients, clinicians, and healthcare policymakers. Rarely, low certainty evidence may lead to strong recommendations. In those instances, we followed generally recommended approaches by the GRADE working group, which are outlined in five paradigmatic situations (e.g., avoiding catastrophic harm) [13]. For recommendations where comparators are not formally stated, the comparison of interest is implicitly referred to as "not using the test". Some recommendations acknowledge current "knowledge gaps" and aim at avoiding premature favorable recommendations for test use and promulgating potentially inaccurate tests.

Revision Process

The draft guideline underwent rapid review for approval by IDSA Board of Directors Executive Committee external to the guideline development panel. The guideline was reviewed and endorsed by ASM, SHEA and PIDS. The IDSA Board of Directors Executive Committee reviewed and approved the guideline prior to dissemination.

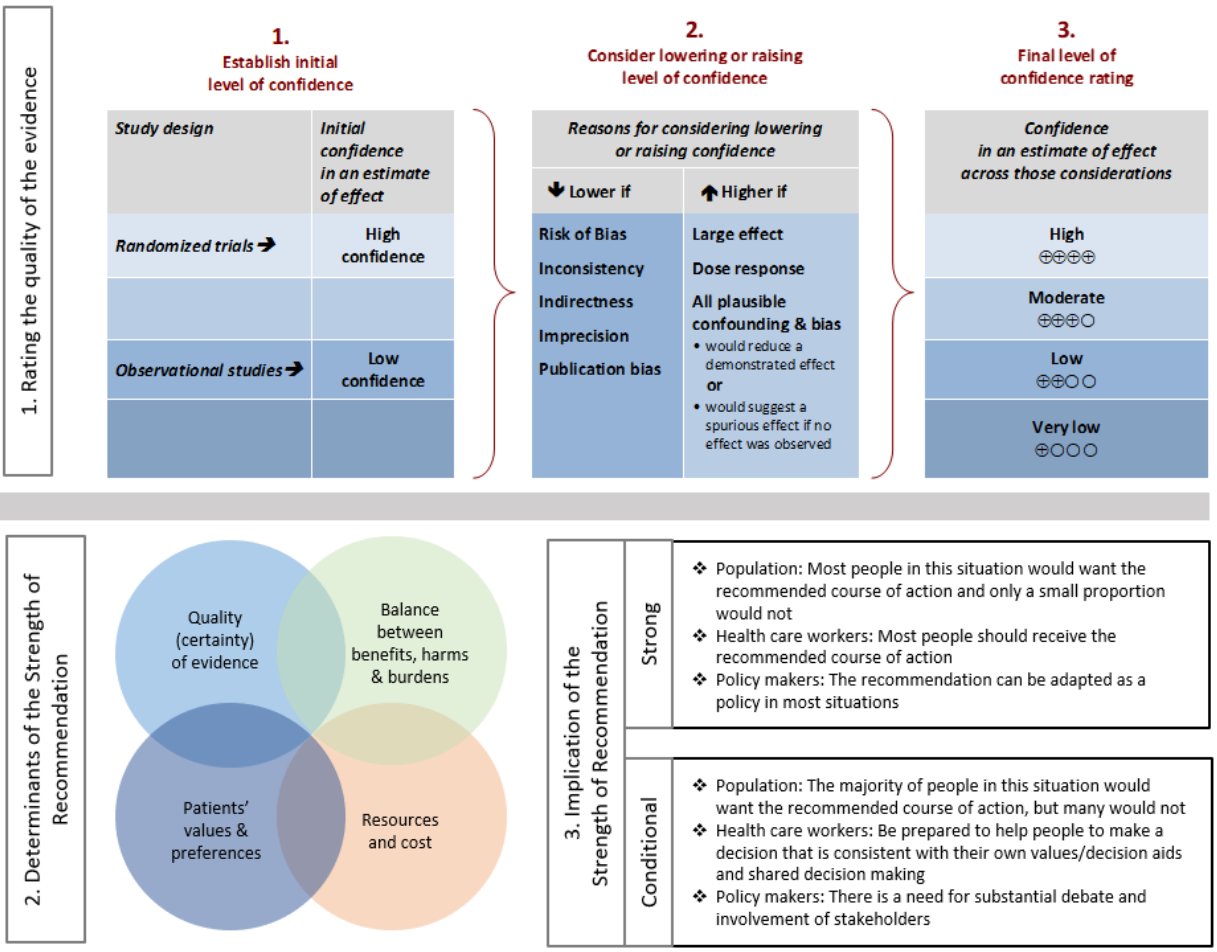
Updating Process

Regular screening of the literature and the COVID-19 situation will take place to determine the need for revisions based on the likelihood that any new data will have an impact on the recommendations. If necessary, the entire expert panel will reconvene to discuss potential changes.

Search Results

A systematic review and horizon scan of the literature identified 2,515 references, 18 of which informed the evidence base for these recommendations (**Figure s1**). Characteristics of the included studies can be found in **Table s3**.

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network)



Recommendations

Standard NAAT vs. Rapid Antigen Tests in Symptomatic Individuals

Recommendation 1: For symptomatic individuals suspected of having COVID-19, the IDSA panel suggests using standard NAAT (either rapid RT-PCR or laboratory-based NAAT) over rapid Ag tests (*conditional recommendation based on moderate certainty in test accuracy of rapid Ag test and very low certainty in comparative test accuracy of rapid RT-PCR* versus *rapid Ag tests*).

Remarks:

- Symptomatic individuals were defined as those with at least one of the common symptoms of COVID-19 (**Table 1, IDSA Guidelines on the Diagnosis of COVID-19: Molecular Diagnostic Testing**).
- If NAAT is not available or results are expected to be delayed beyond 2 – 3 days, rapid Ag testing could be considered.
- For optimal performance, Ag tests should be used within seven days of symptom onset.
- If clinical suspicion for COVID-19 remains high, negative Ag results should be confirmed by standard NAAT.
- Infectiousness of an individual cannot be determined based on Ag testing or NAAT results.

Summary of the evidence

We reviewed the literature systematically to identify studies comparing Ag testing to standard NAAT for the diagnosis of COVID-19 in individuals with symptoms of SARS-CoV-2 infection. We identified 12 studies that evaluated the diagnostic accuracy of Ag testing as compared to NAAT as a reference test in symptomatic individuals (**Table s3**). The studies included 1,060 individuals for sensitivity and 3,528 for specificity [14-25]. We conducted

subgroup analyses based on time since symptoms onset (i.e., less than seven days *versus* more than seven days). Additional subgroup analyses were performed based on different age groups (adults *versus* pediatric patients), transport media (use of viral transport media *versus* direct testing) and instrument produced *versus* visually interpreted results. We also conducted a sensitivity analysis limited to cohort studies as a preferred study design for evaluating diagnostic test accuracy. The overall and subgroup test accuracy data are reported in **Figures s2-s5**. The test accuracy data in symptomatic patients are reported in **Figures s6-s12**. Pooled diagnostic test accuracy measures did not differ in any of the subgroup or sensitivity analyses except for the assessment of time post-symptom onset.

Four of the included studies reported the positive and negative percent agreement between Ag, standard NAAT and viral culture [22, 23, 26, 27]. All of these studies performed viral cultures on samples that were positive based on Ag and/or NAAT and culture were not performed when both Ag and NAAT were negative. Positive and negative percent agreements between antigen and culture are presented in (**Figures s13a-s13b**). We considered 5%, 20%, and 30% as pre-test probabilities for patients presenting with at least one of the most common symptoms of COVID-19. The test accuracy data for NAAT are reported in **Figure s14** and **Table 3** [28].

The certainty of evidence for diagnostic accuracy of Ag ranged from moderate to high depending on the presence of unexplained inconsistency. Subgroup analyses, other than the time of testing post-symptom onset, failed to provide an explanation for any reported inconsistency between studies.

Benefits and harms

The panel considered minimizing the number of false negative COVID-19 diagnoses in symptomatic patients to be a priority. Standard NAAT has a higher positive percent agreement (PPA) with culture than does Ag testing (100% vs 90%, respectively) (**Figures s13a-s13b**). The difference in sensitivity between NAAT and Ag testing is more evident when standard NAAT is used as the reference standard. In these studies, Ag testing had a pooled sensitivity of 81% *versus* NAAT (**Table 2**, **Figure s6a**). With this sensitivity, the number of false negative Ag results

ranges from 9 to 57 per 1,000 individuals tested when the pre-test probability ranges from 5 to 30% (Table 2). Using Ag tests increases the number of false negative results, which could delay a diagnosis of COVID-19 and lead to spread of the virus as well as lead to missed treatment opportunities for infected individuals. The sensitivity of Ag testing increased to 84% when testing was performed within the first seven days of symptom onset (**Figure s9a**). It is important to emphasize that Ag testing had a very high specificity when using NAAT as the reference standard. There is little concern for false positive Ag results for symptomatic individuals, even when the pre-test probability is as low as 5% (Table 2). When standard NAATs are unavailable, or when results are expected to be delayed beyond 2-3 days, rapid Ag tests could be an acceptable alternative for symptomatic patients. An advantage of rapid Ag testing is that positive results are available while the patient is still present, allowing management decisions to be made quickly.

Additional considerations

Standard NAAT, which includes rapid RT-PCR and laboratory-based molecular methods, is the gold standard for diagnosis of viral respiratory infections due to sensitivity, speed, and ease of use compared to culture. However, studies comparing Ag testing and NAAT to culture were included in our analysis because this allowed a direct comparison of Ag and NAAT to an independent method. Given that culture is not the gold standard (poor sensitivity), we reported comparisons across methods as positive and negative percent agreement rather than sensitivity and specificity, respectively (**Figures s13a-s13b**). Assessing performance of Ag tests using culture falsely increased their apparent sensitivity; the positive percent agreement of Ag compared to culture was 90% as compared to a sensitivity of 82% *versus* NAAT. The low negative percent agreement between Ag and culture (71%) is due to the poor sensitivity of culture. This is even more apparent when comparing NAAT to culture; there the negative percent agreement is 23%, showing that NAAT is much more sensitive than culture. Another significant observation from these studies is that 10% of culture positive samples were negative by Ag testing. This is important, as there is a growing opinion that individuals with NAAT-positive/Ag-negative test results are not infectious or that infected individuals who are Ag-negative are unlikely to spread the infection to others. While it is assumed that most culture-

positive individuals are potentially infectious to others, it cannot be concluded that individuals that are either culture-negative or antigen-negative are not infectious.

There was significant heterogeneity in specimen collection methods across studies. Most studies used LFA assays to test swab samples directly without transport media. Direct testing is less complicated and avoids specimen dilution in media, which theoretically increases sensitivity. However, a significant sensitivity difference between direct testing *versus* testing using media or other fluid was not observed in our subgroup analysis (**Figure s5e**). It may be that dilution in media does not significantly affect sensitivity. There may also be confounding factors such as the fact that varieties of different sample types were used across studies (e.g., anterior nasal, mid-turbinate, nasopharyngeal, and oral/nasal swabs). Based on studies of NAATs, the sensitivity of these various samples is not equivalent [28]. It is also imperative to note that the NAAT comparator assay varied across studies and that all used some form of laboratory-based molecular testing. We did not identify any direct comparisons of Ag testing to rapid RT-PCR in symptomatic patients. However, previous comparisons between rapid RT-PCR and laboratory-based NAAT suggest that these groups of tests perform similarly [28].

Conclusions and research needs for this recommendation

Testing continues to be recommended for individuals with COVID-like symptoms irrespective of vaccination status. The committee suggested the use of standard NAATs over rapid Ag tests for symptomatic patients due to their higher sensitivity, thus reducing the risk of missing SARS-CoV-2 infections. However, regardless of the lower sensitivity of Ag tests, they will continue to be used due to their ease of use, rapid results, low cost, and availability. Testing individuals within the first seven days of symptom onset optimizes the sensitivity of rapid Ag tests. If Ag tests are used for testing symptomatic individuals, a negative test result should be confirmed with a standard NAAT when the clinical suspicion for COVID-19 is high. Alternatively, given the high specificity of Ag tests, a positive test result does not require routine confirmation.

Future research should include rigorously designed studies in symptomatic patients including special populations such as immunocompromised hosts. A wider array of Ag tests

should also be evaluated, with assessments of the potential impact of virus variants on test performance. Peer-reviewed studies assessing the performance of self-testing at home are also needed. There is a great need to identify a marker of infectivity. Finally, ensuring equal access to accurate, affordable and timely SARS-CoV-2 diagnostic testing for underserved populations, including racial and ethnic minority groups, should be a priority.

Table 2. Diagnostic test accuracy of rapid antigen test(s) using NAAT(s) as a reference standard in symptomatic patients

Sensitivity: 0.81 (95% CI: 0.72 to 0.88) **Specificity:** 0.99 (95% CI: 0.99 to 1.00)											
Outcome	**№ of studies (№ of patients)**	**Study design**	**Factors that may decrease certainty of evidence**					**Effect per 1,000 patients tested**			**Test accuracy CoE**
			Risk of bias	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**pre-test probability of 5%**	**pre-test probability of 20%**	**pre-test probability of 30%**	
True positives (patients with SARS-CoV-2 infection)	12 studies 1060 patients	cohort & case-control type studies	not serious	not serious	serious[a]	not serious	none	41 (36 to 44)	162 (144 to 176)	243 (216 to 264)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having SARS-CoV-2 infection)								9 (6 to 14)	38 (24 to 56)	57 (36 to 84)	
True negatives (patients without SARS-CoV-2 infection)	12 studies 3528 patients	cohort & case-control type studies	not serious	not serious	not serious	not serious	none	950 (941 to 950)	800 (792 to 800)	700 (693 to 700)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having SARS-CoV-2 infection)								0 (0 to 9)	0 (0 to 8)	0 (0 to 7)	

NAAT: Nucleic acid amplification test; **CI**: Confidence interval; **CoE**: Certainty of evidence

Explanations

a. The point estimates ranged from 0.41 to 0.98.

Table 3. GRADE Evidence Profile of Test Accuracy Results for Prevalence/Pre-Test Probability of 5%, 20%, and 30%, for rapid RT-PCR and standard non-rapid laboratory-based NAAT vs. composite reference standard

	Rapid RT-PCR	Standard laboratory based NAAT
Sensitivity	**0.98 (95% CI: 0.95 to 1.00)**	0.98 (95% CI: 0.95 to 0.99)
Specificity	**0.97 (95% CI: 0.89 to 0.99)**	0.97 (95% CI: 0.92 to 0.99)

Outcome	**№ of studies (№ of patients)**	**Study design**	**Factors that may decrease certainty of evidence**					**Effect per 1,000 patients tested**						**Test accuracy CoE**
								pre-test probability of 5%		**pre-test probability of 20%**		**pre-test probability of 30%**		
			Risk of bias	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**rapid PCR tests**	**standard NAAT**	**rapid PCR tests**	**standard NAAT**	**rapid PCR tests**	**standard NAAT**	
True positives (patients with SARS-CoV-2 infection)	4 studies 230 patients	cohort & case-control type studies	not serious	not serious	serious [b]	not serious [b]	none	49 (48 to 50)	49 (48 to 50)	196 (190 to 200)	196 (190 to 198)	294 (285 to 300)	294 (285 to 297)	⨁⨁⨁◯ MODERATE
								0 fewer TP in rapid PCR test		**0 fewer TP in rapid PCR test**		**0 fewer TP in rapid PCR test**		
False negatives (patients incorrectly classified as not having SARS-CoV-2 infection)								1 (0 to 2)	1 (0 to 2)	4 (0 to 10)	4 (2 to 10)	6 (0 to 15)	6 (3 to 15)	
								0 fewer FN in rapid PCR test		**0 fewer FN in rapid PCR test**		**0 fewer FN in rapid PCR test**		
True negatives (patients without SARS-CoV-2 infection)	4 studies 164 patients	cohort & case-control type studies	not serious	not serious	serious [c]	not serious [c]	none	922 (846 to 941)	922 (874 to 941)	776 (712 to 792)	776 (736 to 792)	679 (623 to 693)	679 (644 to 693)	⨁⨁⨁◯ MODERATE
								0 fewer TN in rapid PCR test		**0 fewer TN in rapid PCR test**		**0 fewer TN in rapid PCR test**		
False positives (patients incorrectly classified as having SARS-CoV-2 infection)								28 (9 to 104)	28 (9 to 76)	24 (8 to 88)	24 (8 to 64)	21 (7 to 77)	21 (7 to 56)	
								0 fewer FP in rapid PCR test		**0 fewer FP in rapid PCR test**		**0 fewer FP in rapid PCR test**		

RT-PCR: Reverse transcriptase polymerase chain reaction; **NAAT**: Nucleic acid amplification test; **CI**: Confidence interval; **TP**: True positives; **FN**: False negatives; **TN**: True negatives; **FP**: False positives; **CoE**: Certainty of evidence

Explanations

a. The study by Bulterys et al which used the Atila iAMP test had a lower sensitivity compared to the other studies, making the range of point estimates 0.92-1.00. Borderline judgment, combined with concerns about imprecision due to the small number of patients, we rated down once only.
b. The study by Smithgall et al which used the Cepheid Xpert Xpress test had a lower sensitivity compared to the other rapid tests, making the range of point estimated 0.92-1.00. Borderline judgment, combined with concerns about imprecision due to the small number of patients, we rated down once only.

References

1. Bulterys PL, Garamani N, Stevens B, et al. Comparison of a laboratory-developed test targeting the envelope gene with three nucleic acid amplification tests for detection of SARS-CoV-2. J Clin Virol **2020**; 129: 104427.
2. Smithgall MC, Scherberkova I, Whittier S, Green DA. Comparison of Cepheid Xpert Xpress and Abbott ID Now to Roche cobas for the Rapid Detection of SARS-CoV-2. J Clin Virol **2020**; 128: 104428.

Single Antigen Test vs. Single Standard NAAT in Asymptomatic Individuals with Risk for Exposure

Recommendation 2: For asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests using a single standard NAAT (either rapid RT-PCR or laboratory-based NAAT) over a single rapid Ag test (*conditional recommendation based on moderate certainty in test accuracy of rapid Ag tests and very low certainty in comparative test accuracy of rapid RT-PCR* versus *rapid Ag tests*).

Remarks:

- SARS-CoV-2 testing in the absence of COVID-like symptoms should be individualized. Vaccination status and history of prior laboratory-confirmed SARS-CoV-2 infection may affect decisions about whether or not to test in certain situations.
- One-time screening at the time of inpatient or long-term care facility admission, or before major surgery, should be done using a rapid RT-PCR or a laboratory-based NAAT. Standard NAATs are desirable for such populations because the higher sensitivity of these methods reduces the likelihood of missing individuals with SARS-CoV-2 infection who could inadvertently expose other vulnerable patients or healthcare personnel. In addition, perioperative SARS-CoV-2 infection may increase risk for pulmonary complications and mortality. Testing can help inform surgical planning.
- One-time screening in community settings (e.g., schools, workplaces, airports) should also ideally be performed using standard NAATs when the pre-test probability is moderate to high (i.e., ≥ 5%). When standard NAAT is not available, rapid Ag testing could be considered.
- One-time testing using NAAT or Ag can be considered in cases of known close contact when the individual cannot be effectively or safely quarantined for 10-14

days. Per current CDC guidance, testing on day 5-7 post-exposure can help inform discontinuation of quarantine as early as day seven [1].

Summary of the evidence

We identified six studies that compared Ag testing to standard NAAT for detection of SARS-CoV-2 infection in asymptomatic patients (**Table s3**). The studies included 501 individuals for sensitivity and 9,866 individuals for specificity [15, 19, 21-23, 29]. The pooled sensitivity for Ag testing was 0.49 (95% confidence interval [CI]: 0.39-0.59) and pooled specificity 1.00 (95% CI: 0.99-1.00) (**Figures s15a-s15b**, Table 5). Subgroup analysis was conducted for different age groups (i.e., adult *versus* pediatric patients). Additional information about Ag and NAAT was abstracted and reported in the Forest plots when available (e.g., testing platform, transport medium and specimen collection sequence). The test accuracy data for the adult and pediatric subgroups are reported in **Figures s16a-s17b**.

Due to lack of direct evidence for asymptomatic individuals with or without known contact with someone with SARS-CoV-2, we applied different pre-test probabilities in the evidence profiles to simulate the two scenarios. We considered 1%, 5%, and 10% as pre-test probabilities for asymptomatic patients without known or suspected contact (Tables 4-5) and 20% and 30% as pre-test probabilities for asymptomatic or pre-symptomatic individuals with known, significant close contact to a person with SARS-CoV-2 infection.

The overall certainty of evidence ranged from moderate to high depending on the presence of unexplained inconsistency. Subgroup analysis failed to provide any explanation for inconsistencies between studies.

Benefits and harms

The panel placed high value on minimizing the number of false negative test results, especially in higher-risk medical settings. Even though rapid Ag testing may be easier to perform and generate results more quickly, for certain populations, including hospitalized patients, residents of long-term care facilities or those undergoing preoperative screening before major surgery, the risks associated with false negative Ag results compared to standard

NAAT are unacceptably high. In these situations, potential spread of infection to other vulnerable patients or healthcare providers could be devastating. In addition, outcomes from major surgery may be worse for patients with SARS-CoV-2 infection [30-33]. Knowing a patient's SARS-CoV-2 infection status before major surgery allows for informed decision-making around optimal timing of the procedure and/or planning for augmented infection prevention measures.

One-time screening in non-clinical settings, such as for return to school or work and before air travel or attendance at a large social gathering, is generally of lower risk. The harms of false negative SARS-CoV-2 testing in these scenarios include missed opportunities to prevent transmission to others and lost contact tracing. Additionally, asymptomatic or pre-symptomatic individuals who receive false negative results may erroneously believe they are not infected and be less likely to adhere to masking and physical distancing recommendations, thus increasing risk for transmission if they are infected. There is also potential harm from falsely positive test results, which include anxiety around inaccurate diagnosis, burden of unnecessary isolation and wasted resources spent on unneeded contact tracing.

To determine the frequency of false negative and positive Ag results compared to standard NAAT in asymptomatic individuals, the panel considered a range of pre-test probabilities for SARS-CoV-2 infection. When the pre-test probability for SARS CoV-2 infection is 1%, the number of true positive Ag results is small and equals the number of false negative results (i.e., five true positives and five false negatives per 1,000 asymptomatic individuals tested) (**Table 4**). Communities and institutions should weigh the resources necessary for screening *versus* the benefits of detecting a few trues cases of SARS CoV-2 infection, especially as vaccination coverage increases or if strategies such as universal masking and distancing will be adhered to regardless of the test result for non-vaccinated individuals. Of note, the number of false positive Ag tests is also expected to be relatively small (range 0-10) when the prevalence is low. Routine confirmation of positive Ag results does not appear necessary in all cases. Alternatively, confirmation of positive Ag tests using standard NAAT may be considered when the pre-test probability or prevalence is very low (e.g., <1%) given the detrimental impact of false positive results, which are more likely to occur in this setting. As the pre-test probability

increases, so does the potential utility of testing. However, Ag testing will continue to result in just as many false negatives as true positives relative to NAAT. When the pre-test probability is 30%, Ag testing detects 147 true infections, but misses 153 per 1,000 asymptomatic individuals tested (Table 5).

Additional considerations

Vaccination status

Increasing evidence suggests that fully vaccinated immunocompetent people are less likely to have asymptomatic SARS-CoV-2 infection. Therefore, considering an individual's vaccination status is important for making decisions about the pre-test probability of infection and the potential utility of programmatic screening.

The CDC recently issued updated guidance for SARS-CoV-2 testing in response to increasing rates of COVID-19 vaccination in the population [34]. Although pre-admission and pre-procedural testing of asymptomatic patients may be of lower yield following vaccination, it can still be useful for informing the type of infection control precautions used (e.g., room assignment, cohorting, and/or the personal protective equipment used). Institutions may elect to continue screening based on the characteristics of the patients they serve. Testing for return to the United States from international destinations continues to be required for air travel regardless of vaccination status. In addition, post-exposure testing following close contact to someone with suspected or confirmed COVID-19 is recommended for fully vaccinated residents and employees of congregate living facilities as well as for vaccinated healthcare providers and hospitalized patients in certain situations.

For instances where testing is being considered for an asymptomatic person with a known or suspected COVID-19 contact within the last 14 days, the timing of testing is also important. Testing too soon, no matter which test is used, may lead to false negative results. Testing may include the use of any NAAT or Ag testing around day 5-7 post-exposure. Negative results can then be used to discontinue quarantine at day seven, assuming no symptoms, if remaining in quarantine for the preferred 10- to 14-day duration is not possible [1]. Using testing on day 5-7 after exposure to exit out of quarantine may reduce burden on individuals

and families as well as potentially increase adherence. Modeling suggests that using negative RT-PCR *versus* negative Ag results to exit quarantine results in similar post-quarantine transmission risk (4.0% residual risk for NAAT [range 2.3-8.6%] vs. 5.5% [range 3.1-11.9%] for Ag) [1]. In addition, a separate model predicted that adding testing at entry to quarantine provided little additional benefit in terms of reduction in post-quarantine transmission risk [35]. However, testing immediately after the last known contact, and then again 5-7 days post-exposure, could be useful for contact tracing efforts. This approach can be considered if testing resources are sufficient and is recommended for asymptomatic healthcare providers and patients or facility residents with higher-risk exposures (regardless of vaccination status).

Asymptomatic individuals without a known close contact by definition have no date of onset of symptoms and no known time from last exposure. Thus, these individuals cannot be tested within an "optimal" time period. Testing too soon or too late after infection may also lead to false negative results, especially if Ag tests are used.

Persistent RNA shedding

SARS-CoV-2 RNA typically remains detectable by sensitive molecular methods for more than two weeks (median 17 days) after the onset of infection, but live virus is not often culturable beyond day nine of illness for non-critically ill immunocompetent individuals [36]. There are potential harms associated with the detection of low levels of SARS-CoV-2 RNA using sensitive molecular methods late in the course of infection. For instance, RNA detection beyond the infectious period might affect return to work decisions and lead to unnecessary isolation that can be a financial burden on individuals, families, and businesses. For these reasons, individuals previously diagnosed with laboratory confirmed COVID-19, who remain asymptomatic after recovery, should generally not be retested within 90 days from the time of symptom onset or first positive viral test [37].

The use of real-time RT-PCR cycle threshold (Ct) values has been proposed as a way to estimate viral load and infer infectiousness to potentially avoid unnecessary isolation. The supposition is that individuals with high Ct values (i.e., low viral loads) are less likely to be infectious to others than are those with low Ct values. However, multiple clinical and analytical

variables affect Ct values (see IDSA/ASM white paper for an overview) and a "threshold" correlating with infectiousness has not been established. While positive Ag test results may identify a subset of individuals with high viral loads, who are more likely to be infectious to others, it must be emphasized that negative Ag testing neither "rules out" infection nor excludes the possibility of infectiousness.

The logistics of testing

Finally, the logistical complexities of scaling up rapid Ag testing for mass screening in the community should not be underestimated. These tests are performed one at a time and managing multiple specimens simultaneously requires several operators with careful technique in concert with a robust plan for specimen tracking. The time required to process large numbers may preclude delivering results in real-time and can be a significant challenge for on-site testing. When molecular diagnostic resources are available, high-throughput testing with laboratory-based NAAT may be easier for some centers to operationalize on a large scale. Mass screening of asymptomatic individuals is one area where pooled NAAT (i.e., combining multiple specimens from different people into a single pool to test as one group) has been shown to increase capacity without significantly reducing sensitivity, particularly when prevalence in the population being tested is relatively low [35, 38]. The downsides of pooling include the need for the laboratory to validate an optimal pool size that maintains test sensitivity combined with a more complex operational workflow. Pools flagged as containing SARS-CoV-2 RNA then need to be tracked and deconvoluted by testing each specimen in the pool individually, which makes test result and specimen tracing more complicated. Pooled testing strategies makes most sense for asymptomatic screening in low to moderate prevalence settings. If the prevalence is too high, the benefits of pooled testing are lost.

Conclusions and research needs for this recommendation

A high number of individuals testing falsely negative is expected to negatively impact public health efforts and be most harmful in medical or long-term care settings. Standard NAAT will detect the most cases of SARS-CoV-2 infection and provide the greatest number of opportunities to prevent transmission compared to currently available Ag tests. The superior

performance of NAAT is expected to have the greatest impact when prevalence in the community is moderate to high (i.e., ≥ 5%). However, use of a less sensitive rapid Ag tests may still be helpful in some lower-risk settings when NAAT is not available. Antigen testing is expected to detect infection when the viral load is high. Additionally, given the high specificity of Ag testing observed across studies of asymptomatic individuals, routine confirmation of positive results may not be necessary in all situations and would have the greatest value when prevalence and pre-test probability are <1% or the potential harms of false positive results are significant. Large-scale studies evaluating the value of Ag *versus* RNA detection in relation to SARS-CoV-2 transmission events are needed, especially as vaccine coverage increases. The development of new Ag tests with increased analytic sensitivity is also of great interest.

Table 4. Diagnostic test accuracy of **single** rapid antigen test(s) using **single** NAAT(s) as a reference standard in **unexposed** asymptomatic individuals

Sensitivity: 0.49 (95% CI: 0.39 to 0.59) **Specificity:** 1.00 (95% CI: 0.99 to 1.00)											
Outcome	**№ of studies (№ of patients)**	**Study design**	**Factors that may decrease certainty of evidence**					**Effect per 1,000 patients tested**			**Test accuracy CoE**
			Risk of bias	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**pre-test probability of 1%**	**pre-test probability of 5%**	**pre-test probability of 10%**	
True positives (patients with SARS-CoV-2 infection)	6 studies 501 patients	cohort & case-control type studies	not serious	not serious	serious[a]	not serious[b]	none	5 (4 to 6)	25 (20 to 30)	49 (39 to 59)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having SARS-CoV-2 infection)								5 (4 to 6)	25 (20 to 30)	51 (41 to 61)	
True negatives (patients without SARS-CoV-2 infection)	6 studies 9866 patients	cohort & case-control type studies	not serious	not serious	not serious	not serious	none	990 (980 to 990)	950 (941 to 950)	900 (891 to 900)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having SARS-CoV-2 infection)								0 (0 to 10)	(0 to 9)	0 (0 to 9)	

NAAT: Nucleic acid amplification test; **CI**: Confidence interval; **CoE**: Certainty of evidence

Explanations

a. The point estimates ranged from 0.33 to 0.67.
b. For 5% pre-test probability, there was serious imprecision as the CI includes the predefined threshold of clinically important false negatives rate (0.2%)

Table 5. Diagnostic test accuracy of **single** rapid antigen test(s) using **single** NAAT(s) as a reference standard in **exposed** asymptomatic individuals

Sensitivity: 0.49 (95% CI: 0.39 to 0.59) **Specificity:** 1.00 (95% CI: 0.99 to 1.00)										
Outcome	**№ of studies (№ of patients)**	**Study design**	**Factors that may decrease certainty of evidence**					**Effect per 1,000 patients tested**		**Test accuracy CoE**
			Risk of bias	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**pre-test probability of 20%**	**pre-test probability of 30%**	
True positives (patients with SARS-CoV-2 infection)	6 studies 501 patients	cohort & case-control type studies	not serious	not serious	serious[a]	not serious	none	98 (78 to 118)	147 (117 to 177)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having SARS-CoV-2 infection)								102 (82 to 122)	153 (123 to 183)	
True negatives (patients without SARS-CoV-2 infection)	6 studies 9866 patients	cohort & case-control type studies	not serious	not serious	not serious	not serious	none	800 (792 to 800)	700 (693 to 700)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having SARS-CoV-2 infection)								0 (0 to 8)	0 (0 to 7)	

NAAT: Nucleic acid amplification test; **CI**: Confidence interval; **CoE**: Certainty of evidence

Explanations

a. The point estimates ranged from 0.33 to 0.67.

Single standard NAAT vs. Two Consecutive Rapid Antigen Tests for Asymptomatic Individuals with Risk for Exposure

Recommendation 3: For asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests a single (i.e., one-time) standard NAAT (either rapid RT-PCR or laboratory-based NAAT) rather than a strategy of two consecutive rapid Ag tests (*conditional recommendation based in moderate certainty in test accuracy of molecular testing and an evidence gap to inform the test accuracy of a strategies using repeat Ag testing*).

Remarks:

- SARS-CoV-2 testing in the absence of COVID-like symptoms should be individualized. Vaccination status and history of prior laboratory-confirmed SARS-CoV-2 infection may affect decisions about whether or not to test in certain situations.
- One-time screening at the time of inpatient or long-term care facility admission or before major surgery should be done using a single rapid RT-PCR or a single laboratory-based NAAT. Standard NAATs are desirable for such populations because the higher sensitivity of these methods reduces the likelihood of missing individuals with SARS-CoV-2 infection that could inadvertently expose other vulnerable patients or healthcare personnel. In addition, perioperative SARS-CoV-2 infection may increase risk for pulmonary complications and mortality. Testing can help inform surgical planning.
- One-time screening in community settings (e.g., schools, workplaces, airports) should also ideally be performed using a single standard NAATs when the pre-test probability is moderate to high (i.e., ≥ 5%). If standard NAATs are not available, performance of a rapid Ag test followed by a second rapid Ag test if the first is negative (i.e., two consecutive tests) could be considered.

- If two rapid Ag tests are performed, sequential testing during the same clinical encounter, when the first test is negative, does not appear to improve sensitivity. The optimal timing between two sequential tests has not been established.

- The strategy of performing two sequential Ag tests only may not apply to facilities experiencing an ongoing outbreak.

Summary of the evidence

We identified a single study comparing two sequential antigen tests *versus* NAAT [39]. This study was conducted as a part of a community testing campaign in which rapid Ag testing was repeated once, within approximately 30 minutes, when the first test was negative. The study included both symptomatic and asymptomatic individuals as well as adults and children. Test positivity was 12.5% for the initial Ag test and 12.7% for the second Ag test *versus* 15.8% for a standard RT-PCR. We also conducted simple modeling to simulate a testing strategy of two sequential Ag tests. An example is provided in **Figure s18a**. Overall, the certainty of the evidence for this recommendation is considered very low due to the indirectness of the evidence used to answer this question.

Benefits and harms

The panel again prioritized minimizing the number of false negative SARS-CoV-2 test results. Rapid RT-PCR and standard laboratory-based NAAT were shown to be significantly more sensitive than Ag testing for asymptomatic individuals (see recommendation #2), with similar performance in adults and children. However, performance of a second rapid Ag test after an initial negative rapid Ag test has the theoretic potential to increase sensitivity. The impact of performing two consecutive antigen tests across a varying range of pre-test probability or prevalence is shown in **Tables 6-7**. Modeling two sequential Ag tests, assuming a pre-test probability of 10%, increased the number of true positives by 25 per 1000 persons tested (**Figure s18b**, **Table 7**). However, increased sensitivity with a second test was contingent on the assumption that the results of each Ag test is independent of the other and not affected by

patient-, specimen- or time-related factors. This is almost certainly an oversimplification of elements influencing clinical test performance. The optimal timing of repeat Ag testing after an initial negative result has not been determined and may vary by the indication for testing. However, in the study by Shah et al., repeating a rapid Ag test within approximately 30 minutes of the first test, when the first test was negative, did not significantly improve sensitivity [39].

Additional considerations

Test subject-specific factors can vary over time. For example, an individual may truly not be infected today, but they may be tomorrow, and testing on both days would be more likely to pick up infection than testing on a single day alone. When there is ongoing risk for exposure, sequential testing over multiple days may be preferred to a strategy of two sequential tests. Although the specificity of a single Ag test was high (100%), repeated testing in low-prevalence settings would be expected to decrease overall specificity slightly (Table 7), thus increasing false positive results. Another limitation of a sequential rapid Ag approach is the possibility of a false negative result relative to NAAT. In addition, screening large numbers of individuals with two rapid Ag tests before an event or travel may be more logistically complex than a single test.

Conclusions and research needs for this recommendation

The IDSA panel's consideration for performing a rapid Ag test followed by a second rapid Ag if the first is negative is based on the assumption that sensitivity could theoretically be increased with two tests. Head-to-head comparison of repeated rapid Ag *versus* a single rapid RT-PCR or a laboratory-based NAAT for screening in asymptomatic individuals is a research priority. Future studies should evaluate the optimal timing between tests in a variety of settings. In addition, studies that assess the test result turn-around-time necessary to make a difference for interventions in real-world practice are needed.

Table 6. Diagnostic test accuracy of **repeat** rapid antigen test(s) using **single** NAAT(s) as a reference standard in **exposed** asymptomatic individuals

Sensitivity: 0.49 (95% CI: 0.39 to 0.59 **Specificity:** 1.00 (95% CI: 0.99 to 1.00)										
Outcome	**№ of studies (№ of patients)**	**Study design**	**Factors that may decrease certainty of evidence**					**Effect per 1,000 patients tested**		**Test accuracy CoE**
			Risk of bias	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**pre-test probability of 20%**	**pre-test probability of 30%**	
True positives (patients with SARS-CoV-2 infection)	6 studies 501 patients	cohort & case-control type studies	not serious	very serious[a]	serious[b]	not serious	none	148 (126 to 166)	222 (188 to 250)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having SARS-CoV-2 infection)								52 (34 to 74)	78 (50 to 112)	
True negatives (patients without SARS-CoV-2 infection)	6 studies 9866 patients	cohort & case-control type studies	not serious	very serious[a]	not serious	not serious	none	800 (784 to 800)	700 (686 to 700)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having SARS-CoV-2 infection)								0 (0 to 16)	0 (0 to 14)	

NAAT: Nucleic acid amplification test; **CI**: Confidence interval; **CoE**: Certainty of evidence

Explanations

a. The estimates were based on simple modeling that assumes repeat testing and no change in prevalence.
b. The point estimates ranged from 0.33 to 0.67

Table 7. Diagnostic test accuracy of **repeat** rapid antigen test(s) using **single** NAAT(s) as a reference standard in **unexposed** asymptomatic individuals

Sensitivity: 0.49 (95% CI: 0.39 to 0.59) **Specificity:** 1.00 (95% CI: 0.99 to 1.00)											
Outcome	**№ of studies (№ of patients)**	**Study design**	**Factors that may decrease certainty of evidence**					**Effect per 1,000 patients tested**			**Test accuracy CoE**
			Risk of bias	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**pre-test probability of 1%**	**pre-test probability of 5%**	**pre-test probability of 10%**	
True positives (patients with SARS-CoV-2 infection)	6 studies 501 patients	cohort & case-control type studies	not serious	very serious[a]	serious[b]	not serious[c]	none	7 (6 to 8)	37 (32 to 42)	74 (63 to 83)	⨁◯◯◯ LOW
False negatives (patients incorrectly classified as not having SARS-CoV-2 infection)								3 (2 to 4)	13 (8 to 18)	26 (17 to 37)	
True negatives (patients without SARS-CoV-2 infection)	6 studies 9866 patients	cohort & case-control type studies	not serious	very serious[a]	not serious	not serious	none	990 (970 to 990)	950 (932 to 950)	900 (882 to 900)	⨁⨁◯◯ VERY LOW
False positives (patients incorrectly classified as having SARS-CoV-2 infection)								0 (0 to 20)	0 (0 to 18)	0 (0 to 18)	

NAAT: Nucleic acid amplification test; **CI**: Confidence interval; **CoE**: Certainty of evidence

Explanations

a. The estimates were based on simple modeling that assumes repeat testing and no change in prevalence.
b. The point estimates ranged from 0.33 to 0.67.
c. For 10% pre-test probability, there was serious imprecision as the CI includes the predefined threshold of clinically important false negatives rate (0.2%).

Single Rapid Antigen Testing vs. No Testing in Asymptomatic Individuals with Risk for Exposure

Recommendation 4: In asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests neither for nor against using single (i.e. one-time) rapid Ag testing over no testing (*evidence gap to inform the utility of Ag testing compared to no testing*).

Remarks:

- SARS-CoV-2 testing in the absence of COVID-like symptoms should be individualized. Vaccination status and history of prior laboratory-confirmed SARS-CoV-2 infection may affect decisions about whether or not to test in certain situations.
- One-time Ag testing (*versus* no testing) can be considered in cases of known close contact when the individual cannot be effectively or safely quarantined for 10-14 days. Per current CDC guidance, testing on day 5-7 post-exposure can help inform discontinuation of quarantine as early as day seven [1].
- One-time Ag testing (*versus* no testing) immediately before an event or travel may be useful for reducing transmission particularly when distancing is not possible, or the ventilation is poor, and community prevalence is moderate to high (i.e., ≥ 5%). In these scenarios, someone who tested positive would be excluded from the event/travel and require isolation, while those who tested negative would still need to adhere to prevention measures such as masking during the event or flight.

Summary of the evidence

There were no studies with direct comparison of single Ag testing to no testing among asymptomatic patients for the diagnosis of SARS-CoV-2 infection. For this reason, we relied on diagnostic test accuracy provided in recommendation #2 to attempt to answer this question.

However, since the comparator here is "no testing", the evidence provided in recommendation #2 is indirect and there is very low certainty in the evidence.

Benefits and harms

The benefits of rapid Ag testing *versus* no testing are different for individuals with known close contact to a person with SARS-CoV-2 infection as compared to those without a known or suspected exposure. For those with known close contact, and no development of symptoms, negative Ag testing at day 5-7 post-exposure can allow exiting quarantine sooner than the recommended 10-14 days. Using an Ag test to exit out of quarantine may reduce burden on individuals and families as well as potentially increase compliance with quarantine, but there is a still a residual transmission risk of approximately 5.5% (range 3.1-11.9%) based on CDC modeling [1]. Using a negative RT-PCR result, performed on day 5-7 post-exposure, to exit quarantine on day seven did not reduce the residual risk for transmission substantially compared to Ag testing (4.0% residual transmission risk for NAAT; range 2.3-8.6%). In addition, a separate model predicted that adding testing at entry to quarantine provided little additional benefit in terms of reduction in post-quarantine transmission risk [35].

The benefits of rapid Ag testing *versus* no testing for asymptomatic individuals without a known exposure is in the identification of otherwise unsuspected infections, which allows immediate initiation of isolation and contact tracing protocols in the case of a positive test. This benefit may be greater for the population at large than for an individual being tested. Given the high specificity of rapid Ag tests, the risk for false positive results, even when the prevalence is low, is relatively small (**Figure s15b**, **Table 6**). The main potential harm involved in the use of rapid Ag testing is that SARS-CoV-2 may not be detected when it is actually present. Antigen testing has the potential to falsely reassure an individual that the individual is not infectious in the case of a false negative, potentially promoting the risk of viral transmission.

The use of a single Ag test for the return of students and teachers to the classroom or for "clearing" on-site work is of interest because of the lower risk presented by a missed positive case, especially if universal masking is adhered to. Similarly, the use of a single rapid Ag test in public settings such as in an airport prior to embarkation or before an indoor gathering

or sporting event has the theoretic potential to stop some asymptomatically infected individuals from exposing others in enclosed spaces where distancing is not possible. However, the actual benefit of one-time testing *versus* no testing in decreasing transmission in schools, businesses, for sports or on public transportation has not been established. When there is significant ongoing risk for exposure to SARS-CoV-2, such as in facilities experiencing an outbreak, repeated testing strategies are generally preferred over one-time or no testing.

Additional considerations

No testing (*versus* Ag or NAAT) may be considered for certain groups of fully vaccinated individuals. According to current CDC guidance, fully vaccinated asymptomatic travelers do not necessarily need a SARS-CoV-2 test around domestic travel or when leaving the United States, unless required by local health authorities [34]. Fully vaccinated individuals may also refrain from routine screening testing (e.g., in the non-medical workplace) when feasible. Most fully vaccinated individuals in the community also do not need to quarantine or undergo testing following close contact to a known or suspected case of COVID-19 because the risk for developing SARS-CoV-2 infection is low [34].

These suggestions are based on what is currently known about vaccine efficacy combined published studies of the performance characteristics of approved Ag tests compared with standard molecular diagnostics tests. Continued introduction of new Ag detection tests and evaluation of testing in diverse settings and populations is ongoing. Antigen tests with improved sensitivity have the potential to change recommendations in the future, as do changes in epidemiology and viral shedding as the pandemic progresses and vaccines are rolled-out. The use of single Ag testing should not be used to supplant the use of the important aspects of symptom screening. Physical distancing and wearing masks also remain important interventions for non-vaccinated individuals.

Conclusions and research needs for this recommendation

The decision to pursue rapid Ag testing *versus* no testing should be individualized and universally accessible to all. Given the relatively low sensitivity of Ag tests, factors to consider

include the potential benefits of identifying a case of SARS-CoV-2 *versus* the potential harms of reporting a falsely negative (or positive) result. The potential to reduce transmission as a result of identifying asymptomatic infections should be weighed against the resources required for mass screening initiatives and account for changes in prevalence that arise with increased vaccine uptake. Further research is required to assess the cost *versus* benefit of Ag screening testing in schools, non-medical workplaces and as a part of pre-travel screening in communities with varying prevalence. It is imperative that equity in access to screening strategies is also considered.

Repeat Rapid Antigen Testing vs. No Testing in Asymptomatic Individuals with Risk for Exposure

Recommendation 5: In asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests neither for nor against using repeat rapid Ag testing over no testing (*evidence gap to inform the utility of a strategy of Ag testing compared to no testing*).

Remarks:

- SARS-CoV-2 testing in the absence of COVID-like symptoms should be individualized. Vaccination status and history of prior laboratory-confirmed SARS-CoV-2 infection may affect decisions about whether or not to test in certain situations.
- Repeat Ag testing (*versus* no testing) is likely to have utility in congregate settings experiencing an outbreak.
- Repeat Ag testing (*versus* no testing) is also expected to detect some asymptomatic infections in populations with moderate to high prevalence (i.e., ≥5%).
- If repeated Ag tests are performed, the optimal number, timing and duration of testing has not been established and may vary by the indication for testing.

Summary of the evidence

There were no studies directly comparing repeated Ag testing to no testing among asymptomatic patients. However, we identified two studies that evaluated a strategy of repeat testing using a EUA Ag test. In the first study, McKay et al. evaluated rapid Ag testing for facility-wide screening of residents and staff during a nursing home outbreak [40]. In a subgroup analysis of 30 individuals with more than one round of paired testing, test performance defined by PPA between Ag and NAAT was similar between symptomatic and asymptomatic individuals (PPA 80% both groups). Whether the asymptomatic group eventually developed symptoms, however, was not reported. In the second study, Vohra et al. concluded that weekly screening of all students, teachers, and staff reduced infections by 50% in high schools and 35% in primary schools [41]. However, this study was observational only (i.e., no control group) and did not provide any information about the trajectory of the pandemic in these locations or assess other measures that may have affected the results.

Benefits and harms

A potential benefit of repeat Ag testing, *versus* no testing, is that despite lower analytic sensitivity compared to standard NAAT, Ag testing should identify individuals with higher viral loads as evidenced by lower RT-PCR Ct values and culture positivity. It is theorized that these individuals might have a higher likelihood of transmitting infection to others. Repeat testing with rapid Ag tests in closed congregate settings has the potential to identify outbreaks early in the population, especially if rapid RT-PCR is not available or results from laboratory-based NAATs are expected to be delayed [40]. In addition, modeling studies have suggested that outbreak control may depend more on frequency of testing and turnaround time to results than analytical test sensitivity [42]. Current CDC guidance suggests considering serial Ag testing (i.e., every 3-7 days) for people that work or reside in long term care facilities experiencing an outbreak, regardless of vaccination status, until no new cases are identified for 14 days [43]. Sequential testing strategies have also been used to screen critical infrastructure workers, athletes and students over time to allow continued participation in face-to -face activities. Empirical data to support these repeated testing approaches, however, are lacking.

The major pitfall of a repeat testing strategy (*versus* no testing) is that it may be harmful at the individual level. Due to the lack of evidence that repeat testing would prevent new infections, deployment of this approach (*versus* no testing) may create a false sense of security that could promote risky behaviors and unnecessary exposures. Furthermore, the lower analytic sensitivity of the rapid Ag tests suggests that applying this approach (*versus* no testing) could be perilous in populations in which missing an infection may cause outbreaks and result in poor outcomes (e.g., hospital units or long-term care facilities with immunocompromised or elderly individuals as well as patients undergoing major surgeries). In the above scenarios, a test with robust sensitivity is likely to be better suited for those populations (see recommendation #2). In settings with low pre-test probability of SARS-CoV-2 infections, repeat Ag testing is likely to yield some false positive results (**Table 7**) creating additional anxiety at the individual level and requiring additional steps for confirmation. Furthermore, real-world experience with repeat testing before an event (prior to availability of COVID-19 vaccines) indicated that such a strategy did not prevent major outbreaks when masks were not required [44].

Additional considerations

The benefit-cost ratio of applying a repeated testing strategy should be considered. The effectiveness of repeat testing will be influenced by prevalence of SARS-CoV-2 in the population combined with the costs for scaling up testing and acting on results. For large screening programs, self-administered tests may be ideal in certain scenarios, but may be more technically and logistically challenging depending on where the testing is performed (e.g., at a testing site *versus* at home). The complexities or costs related to accessing repeated testing could also put underserved populations at risk and increase societal disparities already exacerbated by the pandemic.

Conclusions and research needs for this recommendation

As the availability of Ag tests increases, a repeat testing strategy may be most useful for outbreak control in closed congregate settings when rapid RT-PCR is not available. Robust data that evaluate the accuracy and impact of sequential Ag testing as compared to no testing in

other populations, and considering vaccination status, is needed. Ideally, future clinical studies should also target lower-risk settings (e.g., schools) that are randomized to a repeat testing strategy *versus* no testing to help control for changes that are also likely to be occurring in the community. The number of confirmed infections in each cohort would be used as the main outcome. Potential secondary outcome measures include assessments of the impact of false positive or negative results at the individual level. It is also imperative that equity in access to sequential testing strategies is considered.

Narrative Summaries of Diagnostics Undergoing Evaluation

Current evidence suggests that most fully vaccinated people are less likely to have asymptomatic SARS-CoV-2 infection or transmit the disease to others [45-47]. However, the impact of vaccination on the efficacy and utility of various testing strategies has not been determined and may change over time. It is possible that ongoing genetic evolution may affect the performance of current Ag tests (and vaccines). The impact of genetic variants on Ag test performance is expected to be influenced by the type of change to the protein(s), the design of the Ag test and the prevalence of the variant in the population. The majority of FDA-EUA tests target the nucleocapsid (N) protein, with one detecting spike (S) protein antigens. Thus, ongoing surveillance with a focus on structural changes in the N or S proteins will be important, recognizing that monitoring the impact of variants on Ag test performance is not as straight forward as for molecular diagnostic tests.

Discussion

Universal access to accurate SARS-CoV-2 testing remains an important part of comprehensive pandemic mitigation strategies that also include behavioral measures, contact tracing, and widespread vaccination. The increasing availability, simplicity and relative low cost of rapid Ag tests have enabled expanded testing initiatives, particularly in non-medical settings. Recent studies demonstrate that rapid SARS CoV-2 Ag tests can be performed accurately,

without the need for highly qualified laboratory personnel, in a variety of community locations such pharmacies, long-term care facilities and schools. Laboratory-based Ag testing is an alternative approach that allows for testing larger numbers of specimens at one time. However, the need for specimen transport to a centralized laboratory diminishes the potential benefits of providing results more quickly at the POC. More performance data were available for rapid Ag test performance than for laboratory-based Ag tests. Based on relatively few studies, the sensitivity and specificity of rapid POC *versus* laboratory-based Ag tests appear to be comparable (**Figures s2a-s2b**).

An important finding of this systematic review is the observation that rapid Ag tests have very high specificity. Early concerns about false positive Ag results have not been borne out in the medical literature [48]. Importantly, many of the studies included in our analysis employed non-medical staff to administer rapid Ag testing in the field. Whether the same accuracy can be achieved with self-testing at home, however, has yet to be definitively determined. Given the high specificity of EUA rapid Ag tests, routine confirmation of positive test results, using standard NAAT may not be necessary. Even when the pre-test probability or prevalence is low (i.e., 1%), the number of false positive Ag results is expected to be small, on the order of 0-10 false positive results per 1,000 individuals tested (Table 5). However, confirmation of positive Ag tests results may be considered on a case-by-case basis when the pre-test probability or prevalence of infection is very low (i.e., <1 %) and/or if the impact of a potential false positive result is deemed to be significant.

In contrast, current EUA SARS CoV-2 Ag tests are less sensitive than standard molecular methods. Sensitivity differences were most apparent in comparisons across groups of symptomatic *versus* asymptomatic individuals. The clinical sensitivity of Ag testing was highest (84%; **Figure s9a**) for symptomatic individuals tested early during the course of illness, which is the time when the virus load is expected to be highest. Test sensitivity dropped to 62% (**Figure s12a**) after more than seven days from the time of symptom onset. Interestingly, the sensitivity of Ag testing in the first week after symptom onset (84%; 95% CI: 75-91) was similar to our previous assessments of rapid isothermal NAAT sensitivity (81%; 95% CI: 75-86). It should be noted that we did not identify any studies directly comparing rapid Ag testing to the ID Now

rapid isothermal NAAT (Abbott) [28]. Most studies reporting on the performance of the ID Now, however, were performed in patients with signs or symptoms of COVID-19 [28]. Antigen test sensitivity was lowest for asymptomatic individuals (49%; **Figure s15a**, Tables 4-5).

We performed multiple additional subgroup analyses to assess the impact of age, test platform and specimen type on Ag test performance. Overall, EUA status Ag tests performed similarly in adults and children regardless of the presence or absence of symptoms (**Figures s3-s4**). Antigen tests that include an instrument readout trended towards having higher sensitivity (82%; 95% CI: 70-89) compared to those that are read visually (69%; 95% CI: 54-81), but the confidence intervals overlapped, which suggests no statistically significant difference (**Figure s5c**). Counterintuitively, using swabs in transport media appeared slightly more sensitive than did testing the swab directly (85% [95% CI: 64-95] *versus* 73% [95% CI: 65-80], **Figure s5e**); but again, the confidence intervals were wide and overlapped. Dilution of the swab in transport media or other fluid would be expected to decrease test sensitivity. It is possible that transport media studies included greater numbers of nasopharyngeal swabs, and as a result, these samples contained higher viral loads.

The isolation of replication competent virus in culture has been used as a surrogate to infer presence of infectious virus in a clinical sample. In our analyses, Ag testing had a 90% positive percent agreement with viral culture (**Figure s13a**). This observation supports the assertion that Ag testing (or rapid isothermal NAAT) should identify most culture positive individuals, and by inference, this would be a group who are more likely to be shedding infectious virus. However, there are several important caveats to emphasize related to the predictive value of Ag testing for determining infectiousness. First, while culture positive specimens were also likely to be Ag positive, culture negativity or Ag negativity does not mean that transmission of infection is not possible. Viral culture is a relatively insensitive method that is also prone to analytical variability across laboratories. Additionally, false negative Ag results were observed in all of the studies that used culture as a comparator (range 3%-21% false negative Ag tests *versus* culture). It is likely that some individuals with SARS-CoV-2 infection who test negative by Ag and/or culture are infectious to others. New tests capable of accurately predicting infectiousness are needed.

Mathematical modeling has suggested that repeated Ag testing will help to overcome the sensitivity limitations and the frequency of testing and turn-around-time to results may be just as important as test sensitivity in certain situations. Well-designed studies are needed to measure the effect of repeated testing strategies on analytic test performance and transmission events in a variety of settings. In addition, the cost-effectiveness of repeated Ag testing *versus* less frequent rapid RT-PCR, or potentially no testing depending on prevalence, needs to be determined. Potential effectiveness measures should include the number of SARS-CoV-2 cases identified, the results of contact tracing around new cases, and ideally, transmission events. In addition to the price of test kits (e.g., reagents and consumables), assessments of cost should also factor the resources required to scale up testing.

Finally, it is important to note that our systematic literature review occurred before the widespread availability of SARS-CoV-2 vaccines. Testing recommendations may change as more individuals are vaccinated and additional data on test performance in vaccinated individuals becomes available. In addition, we only included studies of Ag tests with FDA-EUA status. Non-EUA tests may perform similarly, better or worse than EUA tests. New tests are also likely to come to market and will need to be evaluated in the future.

Conclusions

Rapid SARS-CoV-2 Ag tests are now available and equal access to testing resources across all communities must be ensured. The ease of use and lower price per test, relative to most commercial molecular methods, are attractive features of rapid Ag testing. Overall, Ag testing had a sensitivity of 81% in symptomatic individuals and 49% in asymptomatic, with specificity of close to ³99% compared to standard NAAT as the comparator. Given the lower sensitivity of Ag tests, standard NAAT remains the diagnostic modality of choice for detecting SARS-CoV-2 infection, especially when the pre-test probability of infection is moderate to high (i.e., ≥ 5%) and/or the harms of false test negative results are significant. In situations where standard NAAT is not available or not feasible, Ag testing could be used without the need to routinely confirm positive test results with NAAT. However, a negative Ag test does not rule out

SARS-CoV-2 infection or infectivity. Negative Ag test results should be confirmed by standard NAAT for patients with signs or symptoms of COVID-19, an approach which is in line with the FDA labeling for these assays.

Notes

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COI Summary

The following list displays what has been reported to the IDSA. To provide thorough transparency, the IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process which includes assessment by the Board of Directors liaison to the Standards and Practice Guideline Committee and, if necessary, the Conflicts of Interest (COI) and Ethics Committee. The assessment of disclosed relationships for possible COI is based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be

interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. **K.H.** serves as an advisor for BioFire and Quideland and receives research funding from the National Institutes of Health (NIH). **A.C.** serves as an advisor for Roche Diagnostics, Danaher, Quidel, First Light, Day Zero, Visby, and Chroma Code; receives research funding from ArcBio and Hologic; and has served as an advisor for Luminex. **C.A.** receives royalties from UpToDate and receives research funding from Merck, MeMed Diagnostics, Entasis Pharmaceuticals and the National Institute of Allergy and Infectious Diseases (NIAID)/NIH. **M.H.** was a co-investigator on a research study for Sage, Medline, and Molnlycke; and received research funding from the Centers for Disease Control and Prevention. **J.E.** serves as a consultant for Sanofi Pasteur; an advisor/consultant for Meissa Vaccines; and receives research funding from the Centers for Disease Control and Prevention (CDC), Brotman Baty Research Institute, Merck, Novavax, GlaxoSmithKline, and AstraZeneca. **M.L.** serves as an advisor for Sanofi, Seqirus, and Medicago; has served as an advisor for Pfizer, Sunovion, and MD Brief; and receives research funding from the Canadian Institutes of Health Research and the Medical Research Council (United Kingdom). **R.P.** receives grants from Shionogi, CD Diagnostics, Merck, Hutchison Biofilm Medical Solutions, Accelerate Diagnostics, ContraFect, and TenNor; serves as a consultant for Curetis, Specific Technologies, Next Gen Diagnostics, Pathoquest, Selux Diagnostics, 1928 Diagnostics, PhAst, and Qvella; holds patent for *B. pertussis/parapertussis* PCR, device/method for sonification, and an anti-biofilm substance; receives research funding from the NIH, the National Science Foundation and the U.S. Department of Defense; and receives monies/reimbursement from the American Society for Microbiology (ASM), the Infectious Diseases Society of America (IDSA), the National Board of Medical Examiners, UpToDate, and the Infectious Disease Board Review Course. **Y.F.Y.** receives honoraria for evidence reviews and teaching from the Evidence Foundation, honoraria for evidence reviews for the American Gastroenterological Association, and serves as a Director for the Evidence Foundation and for the U.S. GRADE Network; and **M.H.M** receives research funding from the Agency for Healthcare Research and Quality (AHRQ), the Endocrine Society, the Society for Vascular Surgery, and The American Society of Hematology and is a Board

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