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Infectious Diseases Society of America G8uidelines on the Diagnosis of COVID-19

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Abstract

Background: Accurate molecular diagnostic tests are necessary for confirming a diagnosis of coronavirus disease 2019 (COVID-19). Direct detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acids in respiratory tract specimens informs patient, healthcare institution and public health level decision-making. The numbers of available SARS-CoV-2 nucleic acid detection tests are rapidly increasing, as is the COVID-19 diagnostic literature. Thus, the Infectious Diseases Society of America (IDSA) recognized a significant need for frequently updated systematic reviews of the literature to inform evidence-based best practice guidance.

Objective: The IDSA's goal was to develop an evidence-based diagnostic guideline to assists clinicians, clinical laboratorians, patients and policymakers in decisions related to the optimal use of SARS-CoV-2 nucleic acid amplification tests. In addition, we provide a conceptual framework for understanding molecular diagnostic test performance, discuss the nuance of test result interpretation in a variety of practice settings, and highlight important unmet research needs in the COVID-19 diagnostic testing space.

Methods: IDSA convened a multidisciplinary panel of infectious diseases clinicians, clinical microbiologists, and experts in systematic literature review to identify and prioritize clinical questions and outcomes related to the use of SARS-CoV-2 molecular diagnostics. 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 15 diagnostic recommendations.

Conclusions: Universal access to accurate SARS-CoV-2 nucleic acid testing is critical for patient care, hospital infection prevention and the public response to the COVID-19 pandemic. Information on the clinical performance of available tests is rapidly emerging, but the quality of evidence of the current literature is considered low to very low. Recognizing these limitations,

the IDSA panel weighed available diagnostic evidence and recommends nucleic acid testing for all symptomatic individuals suspected of having COVID-19. In addition, testing is recommended for asymptomatic individuals with known or suspected contact with a COVID-19 case. Testing asymptomatic individuals without known exposure is suggested when the results will impact isolation/quarantine/personal protective equipment (PPE) usage decisions, dictate eligibility for surgery, or inform administration of immunosuppressive therapy. Ultimately, prioritization of testing will depend on institutional-specific resources and the needs of different patient populations.

IDSA Disclaimer

It is important to realize that guidelines cannot always account for individual variation among patients. They are assessments of current scientific and clinical information provided as an educational service; are not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); should not be considered inclusive of all proper treatments methods of care, or as a statement of the standard of care; do not mandate any particular course of medical care; and are not intended to supplant physician judgment with respect to particular patients or special clinical situations. Whether and the extent to which to follow guidelines is voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances. While IDSA makes every effort to present accurate, complete, and reliable information, these guidelines are presented "as is" without any warranty, either express or implied. IDSA (and its officers, directors, members, employees, and agents) assume no responsibility for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with these guidelines or reliance on the information presented.

Executive Summary

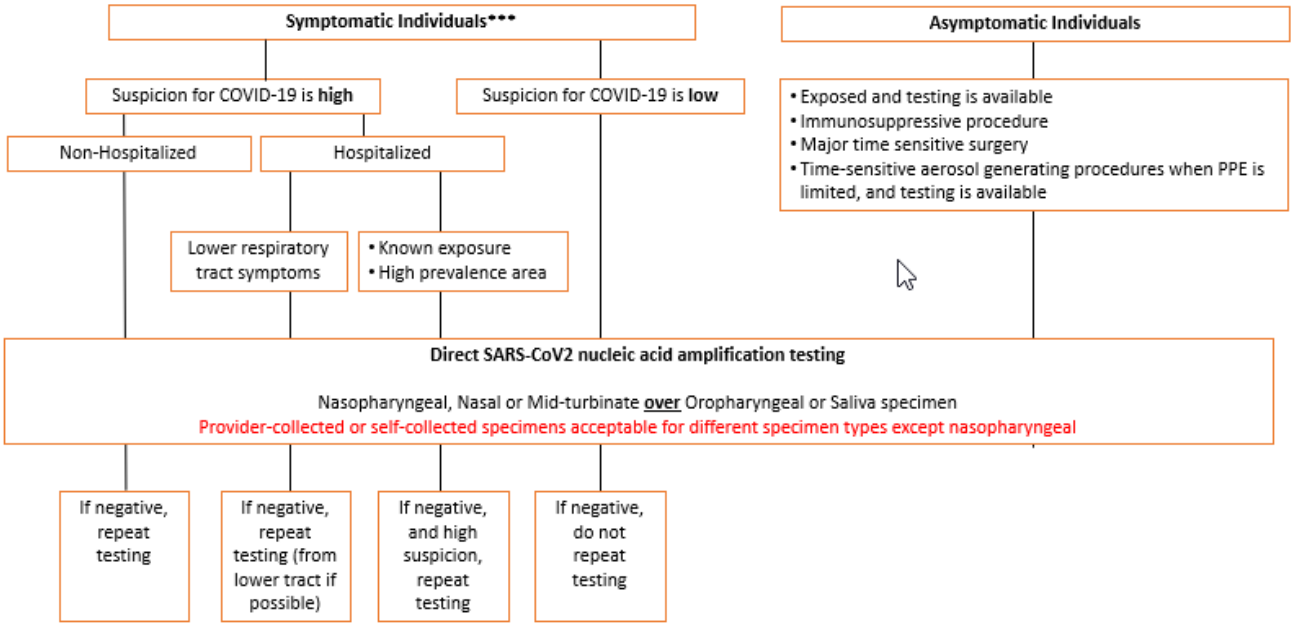
Molecular diagnostic testing has played a critical role in the global response to the COVID-19 pandemic. Accurate SARS-CoV-2 nucleic acid amplification tests (NAATs) are needed to inform patient management decisions, hospital infection prevention practices, and public health responses. Additionally, detection and quantification of SARS-CoV-2 RNA over the course of infection is also essential for understanding biology of disease. Given the rapid expansion of the COVID-19 molecular diagnostic literature along with increasing test availability, the IDSA recognized the need for frequently updated, evidence-based guidelines to support clinicians, clinical microbiologists, patients and policy makers in decisions related to the use of SARS-CoV-2 diagnostics.

Summarized below are 15 recommendations for SARS-CoV-2 nucleic acid testing based on systematic reviews of the diagnostic literature. An algorithm based on these recommendations is provided as well to aid in decision-making (see **Figure 1**). Primary recommendations assumed availability of diagnostic tests and specimen collection devices. Contingency recommendations were crafted for situations where testing supplies or personal protective equipment (PPE) are limited. Based on reviews of baseline risk, assumptions were made about COVID-19 disease

prevalence in the community and/or pretest probabilities in individual patients, both of which influenced testing recommendations.

A detailed description of background, methods, evidence summary and rationale that support each recommendation, and research needs can be found online in the full text. Briefly, an expert panel consisting of clinicians, medical microbiologists and methodologists critically appraised the COVID-19 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 strong recommendations and "suggest" implies conditional recommendations.

Figure 1. IDSA Algorithm for SARS-CoV-2 Nucleic Acid Testing



- Testing should be prioritized for symptomatic patients first.
- When resources are adequate, testing for selected asymptomatic individuals can also be considered.

Recommendation 1. The IDSA panel recommends a SARS-CoV-2 nucleic acid amplification test (NAAT) in symptomatic individuals in the community suspected of having COVID-19, even

when the clinical suspicion for COVID-19 is low (strong recommendation, very low certainty of evidence).

Remarks:

- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).
- Clinical assessment alone is not accurate in predicting COVID-19 diagnosis.
- The panel considered timeliness of SARS-CoV-2 NAAT results essential to impact individual care, healthcare institution, and public health decisions. In the outpatient setting, results within 48 hours of collection is preferable.

Recommendation 2: The IDSA panel suggests collecting nasopharyngeal, or mid-turbinate, or nasal swabs rather than oropharyngeal swabs or saliva alone for SARS-CoV-2 RNA testing in symptomatic individuals with upper respiratory tract infection (URTI) or influenza like illness (ILI) suspected of having COVID-19 (conditional recommendation, very low certainty of evidence).

Remark:

- This recommendation does not address testing a combination of specimen types due to lack of evidence.
- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Recommendation 3. The IDSA panel suggests that nasal and mid-turbinate (MT) swab specimens may be collected for SARS-CoV-2 RNA testing by either patients or healthcare providers, in symptomatic individuals with upper respiratory tract infection (URTI) or influenza like illness (ILI) suspected of having COVID-19 (conditional recommendation, low certainty of evidence).

Remarks:

- Appropriate specimen collection and transport to the laboratory is critical. General instructions for swab-based SARS-CoV2 testing are shown in **Table 4**. Additional resources are available on the IDSA website.
- A clear, step-by-step protocol needs to be presented to patients attempting self-collection. This could be in the form of a short video or printed pamphlet with illustrations.
- The majority of self-collection studies were performed in the presence of a healthcare worker.
- The available evidence for nasal and MT swabs as alternatives to healthcare personnel collection is based on assessment of symptomatic patients. Data on self-collection in asymptomatic individuals is currently unavailable.
- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Recommendation 4: The IDSA panel suggests a strategy of initially obtaining an upper respiratory tract sample (e.g., nasopharyngeal swab) rather than a lower respiratory sample for SARS-CoV-2 RNA testing in hospitalized patients with suspected COVID-19 lower respiratory tract infection. If the initial upper respiratory sample result is negative, and the suspicion for disease remains high, the IDSA panel suggests collecting a lower respiratory tract sample (e.g., sputum, bronchoalveolar lavage fluid, tracheal aspirate) rather than collecting another upper respiratory sample (conditional recommendations, very low certainty of evidence).

Remark:

- The panel considered timeliness of SARS-CoV-2 NAAT results essential to impact individual care and isolation decisions. In the hospital setting, results within 24 hours of collection is preferable.

Recommendation 5: The IDSA panel suggests performing a single viral RNA test and not repeating testing in symptomatic individuals with a low clinical suspicion of COVID-19 (conditional recommendation, low certainty of evidence).

Remarks:

- A low clinical suspicion should be informed by epidemiological information available for the region coupled with clinical judgment.
- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Recommendation 6: The IDSA panel suggests repeating viral RNA testing when the initial test is negative (*versus* performing a single test) in symptomatic individuals with an intermediate or high clinical suspicion of COVID-19 (conditional recommendation, low certainty of evidence).

Remarks:

- Intermediate/high clinical suspicion typically applies to the hospital setting and is based on the severity, numbers and timing of compatible clinical signs/symptoms.
- Repeat testing should generally occur 24-48 hours after initial testing and once the initial NAAT result has returned as negative.
- Another specimen type, preferably a lower respiratory tract specimen if the patient has signs/symptoms of LRTI, should be considered for repeat testing.
- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Recommendation 7: The IDSA panel makes no recommendations for or against using rapid (i.e., test time ≤ 1hour) versus standard RNA testing in symptomatic individuals suspected of having COVID-19 (knowledge gap).

Recommendation 8: The IDSA panel suggests SARS-CoV-2 RNA testing in asymptomatic individuals who are either known or suspected to have been exposed to COVID-19 (conditional recommendation, very low certainty of evidence).

Remarks:

- Known exposure was defined as direct contact with a laboratory confirmed case of COVID-19.
- Suspected exposure was defined as working or residing in a congregate setting (e.g., long-term care, correctional facility, cruise ship, factory, among others) experiencing a COVID-19 outbreak.
- The risk of contracting SARS-CoV-2 may vary under different exposure conditions.
- This recommendation assumes the exposed individual was not wearing appropriate PPE.
- The decision to test asymptomatic patients will be dependent on the availability of testing resources.

Recommendation 9: The IDSA panel suggests against SARS-CoV-2 RNA testing in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a low prevalence of COVID-19 in the community (conditional recommendation, very low certainty of evidence).

Remarks:

- Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19.
- A low prevalence of COVID-19 in the community was considered communities with a prevalence of <2%.
- This recommendation does not apply to immunocompromised individuals.
- This recommendation does not apply to individuals undergoing time-sensitive major surgery or aerosol generating procedures.

Recommendation 10: The IDSA panel recommends direct SARS-CoV-2 RNA testing in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a high prevalence of COVID-19 in the community (i.e., hotspots) (conditional recommendation, very low certainty of evidence).

Remarks:

- Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19.
- A high prevalence of COVID-19 in the community was considered communities with a prevalence of ≥10%.
- The decision to test asymptomatic patients (including when the prevalence is between 2 and 9%) will be dependent on the availability of testing resources.

Recommendation 11: The IDSA panel recommends for SARS-CoV-2 RNA testing in immunocompromised asymptomatic individuals who are being admitted to the hospital regardless of exposure to COVID-19 (strong recommendation, very low certainty of evidence).

Remarks:

- This recommendation defines immunosuppressive procedures as cytotoxic chemotherapy, solid organ or stem cell transplantation, long acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids.

Recommendation 12: The IDSA panel recommends SARS-CoV-2 RNA testing (*versus* no testing) in asymptomatic individuals before immunosuppressive procedures regardless of a known exposure to COVID-19 (strong recommendation, very low certainty of evidence).

Remarks:

- This recommendation defines immunosuppressive procedures as cytotoxic chemotherapy, solid organ or stem cell transplantation, long acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids.
- Testing should ideally be performed as close to the planned treatment/procedure as possible (e.g. within 48-72 hours).

- Many of these patients require frequent, repeated or prolonged visits to receive treatment.
- This recommendation does not address risks or strategies to deal with SARS-CoV-2 transmission in outpatient settings such as infusion centers.

Recommendation 13: The IDSA panel suggests for SARS-COV-2 RNA testing in asymptomatic individuals (without known exposure to COVID-19) who are undergoing major time-sensitive surgeries (conditional recommendation, very low certainty of evidence).

Remarks:

- The panel defined time-sensitive surgery as medically necessary surgeries that need to be done within three months**.**
- Testing should ideally be performed as close to the planned surgery as possible (e.g. within 48-72 hours).
- To limit potential poor outcomes, deferring non-emergent surgeries should be considered for patients testing positive for SARS-CoV-2.
- Decisions about PPE use for the aerosol generating portions of these procedures may be dependent on test results when there is limited availability of PPE. However, there is a risk for false negative test results, so caution should be exercised by those who will be in close contact with/exposed to the upper respiratory tract (e.g., anesthesia personnel, ENT procedures).
- The decision to test asymptomatic patients will be dependent on the availability of testing resources.
- This recommendation does not address the need for repeat testing if patients are required to undergo multiple surgeries over time.

Recommendation 14: The IDSA panel suggests against SARS-CoV-2 RNA testing in asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when PPE is available (conditional recommendation, very low certainty of evidence).

Remarks:

- The panel defined time-sensitive procedures as medically necessary procedures that need to be done within three months**.**
- Procedures considered to be aerosol generating are listed in **Table 9**.

Recommendation 15: The IDSA panel suggests SARS-CoV-2 RNA testing in asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when PPE is limited, and testing is available (conditional recommendation, very low certainty of evidence).

Remark:

- The panel defined time-sensitive procedures as medically necessary procedures that need to be done within three months**.**
- Testing should be performed as close to the planned procedure as possible (e.g. within 48-72 hours).
- Decisions about PPE will be dependent on test results because of limited availability of PPE. However, there is a risk for false negative test results, so caution should be exercised for those who will be in close contact with/exposed to the patient's airways.
- Procedures considered to be aerosol generating are listed in **Table 9**.
- The decision to test asymptomatic patients will be dependent on the availability of testing resources.
- This recommendation does not address the need for repeat testing if patients are required to undergo multiple procedures over time.

Background

In late December 2019, an outbreak of pneumonia cases of unclear etiology was reported in Wuhan City, Hubei Province, China [1]. Unbiased next generation sequencing (NGS) using lower respiratory tract (LRT) specimens collected from affected patients subsequently identified a novel coronavirus as the cause of illness now known as Coronavirus Disease 2019 (COVID-19). The entire viral genome was shared online within days and phylogenetic analyses established close relationship to human severe acute respiratory syndrome coronavirus (SARS-CoV) as well as several other SARS-like bat coronaviruses [1, 2]. Based on genetic similarities, the novel coronavirus was officially named SARS-CoV-2 [3]. By March 11th, 2020, the virus had spread to at least 114 countries and killed more than 4,000 people, prompting the World Health Organization (WHO) to officially declare a global pandemic [4].

Public availability of the SARS-CoV-2 genome was an essential first step enabling development of accurate molecular diagnostic assays. Nucleic acid amplification tests (NAATs) designed to detect one or more gene sequences specific to SARS-CoV-2 are essential for confirming COVID-19 diagnoses. On February 4th, 2020, the United States (U.S.) Secretary of Health and Human Services announced that circumstances existed justifying authorization of the emergency use of SARS-CoV-2 molecular tests. This declaration meant that commercial manufacturers and clinical laboratories were required to submit details about their SARS-CoV-2 assays to the U.S. Food and Drug Administration (FDA) for review and emergency use authorization (EUA).

To date, multiple commercial test manufacturers and clinical laboratories, including academic medical centers, have received EUA for a SARS-CoV-2-specific molecular diagnostic test. The first home-based test collection kit was also recently granted an EUA [5]. It is important to recognize, however, that EUA guidance differs substantially from the standard FDA approval process. In the setting of a public health emergency, the FDA only requires test developers to establish acceptable analytical accuracy. Clinical test performance (i.e., sensitivity and specificity) has yet to be determined or comprehensively compared across EUA platforms. As a result, most of the NAAT performance data used to inform this guideline was derived from

studies evaluating assays not widely used in the U.S. We assumed, therefore, that performance of standard NAAT methods to be comparable across countries (which may or may not be correct).

Given increasing test availability combined with a rapidly growing number of NAAT-focused studies published online or in academic journals, the Infectious Diseases Society of America (IDSA) formed a multidisciplinary panel to critically appraise the existing literature and develop evidence-based diagnostic test recommendations. The panel identified and prioritized practical diagnostic questions pertaining to symptomatic patients and asymptomatic individuals to drive the literature review. The symptoms considered compatible with COVID-19 are listed in **Table 1**.

At the time of this review, there was little evidence to inform use of serologic testing. Therefore, the first version of the IDSA diagnostic guideline focuses only on the use of targeted NAAT applied directly respiratory tract specimens. It is anticipated that these guidelines will be frequently updated as substantive new information becomes available; subsequent versions will also address SARS-CoV-2 serology due to the rapidly evolving information and uncertainty of the reliability of serological tests.

Table 1. Symptoms Compatible with COVID-19

Symptoms may appear **2-14 days after exposure to the virus.** People with these symptoms or combinations of symptoms may have COVID-19*	*Respiratory symptoms alone* • Cough • Shortness of breath or difficulty breathing *Or at least two of these symptoms* • Fever • Chills • Repeated shaking with chills • Muscle pain • Headache • Sore throat • New loss of taste or smell

Children have similar symptoms to adults and generally have mild illness.
*This list is not all inclusive.
Centers for Disease Control and Prevention. Symptoms of Coronavirus. Available at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed 3 May 2020.

Methods

This guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for evidence assessment. In addition, given the need for rapid response to an urgent public health crisis, the methodological approach was modified according to the GIN/McMaster checklist for development of rapid recommendations [6].

Panel Composition

The panel was composed of 8 members including frontline clinicians, infectious diseases specialists and clinical microbiologists who were members of the IDSA, American Society for Microbiology (ASM), Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS). They represented the disciplines of adult and pediatric infectious diseases, medical microbiology, as well as nephrology and gastroenterology. The Evidence Foundation provided technical support and guideline methodologists for the development of this guideline.

Disclosure and Management of Potential Conflict of Interest (COI)

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 conflicts of interest, 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 COI 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 potential relevant

(related to the topic) conflicts. The chair and all members of the technical team were determined to be unconflicted.

Question Generation

Clinical questions were developed into a Population, Intervention, Comparison, Outcomes (PICO) format [7] prior to the first panel meeting (**Table s1**). IDSA panel members prioritized questions with available evidence that met the minimum acceptable criteria (i.e., the body of evidence reported on at least test accuracy results can be applied to the population of interest). Panel members prioritized patient-oriented outcomes related to SARS-CoV-2 testing such as requirement for self-quarantine, eligibility for investigational COVID-19 treatment, timing of elective surgery or procedures, and management of immunosuppressive therapy. We also considered the impact of SARS-CoV-2 results on infection prevention and public health practices, including the use of personal protective equipment (PPE) and contact tracing.

Search Strategy

The National Institute of Health and Care Excellence (NICE) and the Center of Disease Control (CDC) highly-sensitive search was reviewed by the methodologist in consultation with the technical team information specialist and was determined to have high sensitivity. An additional term, COVID, was added to the search strategy used in addition to the terms identified in the PICO questions (**Table s2**). Ovid Medline and Embase were searched from 2019 through April 20, 2020. Horizon scans were performed daily during the evidence assessment and recommendation process to locate additional grey literature and manuscript preprints from the following sources Litcovid, Medrxiv, SSRN, and Trip database. Reference lists and literature suggested by panelists were reviewed for inclusion. No restrictions were placed on language or study type.

Screening and Study Selection

Two reviewers independently screened titles and abstracts, as well as eligible full-text studies. We included studies reporting data on diagnostic test accuracy (cohort studies, cross sectional

studies and case-control studies). When questions compared the performance of different tests (e.g., different testing or sampling methods) or testing strategies, we included studies that provided direct test accuracy data about both tests in the same population. When these direct studies where lacking, we included studies that assessed a single test and compared its results to a reference standard. We did not limit our inclusion to a specific reference standard due to sparsity of data. We also included studies that assessed the prevalence of COVID-19 in different populations. Reviewers extracted relevant information into a standardized data extraction form.

Data Collection and Analysis

Two reviewers completed data extraction independently and in duplicate. Disagreements were resolved by discussion to reach consensus and in consultation with expert clinician scientists. Data extracted included general study characteristics (authors, publication year, country, study design), 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). Accuracy estimates from individual studies were combined quantitatively (pooled) for each test using *OpenMetaAnalyst* (http://www.cebm.brown.edu/openmeta/). We had planned to conduct a bivariate analysis for pooling sensitivity and specificity for each of the test comparisons to account for variation within and between studies. However, this was not feasible due to the sparsity of available data and lack of information on specificity in most instances, so we either presented data as a range of the extreme sensitivity and specificity presented in the studies or pooled as proportions to facilitate decision making. We had also planned to use the Breslow-Day test to measure the percentage of total variation across studies due to heterogeneity (I^2) but were not able to do that due to the sparsity of data. Forest plots were created for each comparison.

To calculate the absolute differences in effects for different testing or sampling strategies, we applied the results of the sensitivity and specificity to a range of plausible prevalence in the population. We then calculated true positives, true negatives, false positives, and false

negatives. To determine the prevalence for each question, we considered the published literature in consultation with the clinical experts. In general, for questions addressing symptomatic individuals we considered the following prevalence: 10% which is typically seen in symptomatic outpatients who have not reached a hospital facility [8-10]; 40% which is typically seen in patients meeting clinical definition for COVID-19 who were hospitalized [11, 12]; and 80% which is typically seen in patients meeting clinical definition for COVID-19 who were admitted to intensive care units. For questions addressing asymptomatic individuals who were exposed to COVID-19, we considered that the prevalence may range from 10% to 50% based on household clusters, nursing home outbreak, active surveillance of passengers quarantined on a cruise ship or passengers of repatriation flights, hospital employees with close contact with COVID-19 positive patients and customers and employees of a restaurant that had a COVID-19 outbreak [13-19]. For questions addressing asymptomatic individuals, we considered that the prevalence may range from <1% in general population who are not in hotspots to 10% in asymptomatic patients in hotspots [8, 20, 21].

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 (**Table s3**) [22]. 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 [23, 24]. GRADE summary of findings tables were developed in GRADEpro Guideline Development Tool [25].

Evidence to Recommendations

The panel considered core elements of the 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 the 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 and "we suggest" indicate conditional recommendations. **Figure 2** 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 a catastrophic harm) [26]. For recommendations pertaining to good practice statements, appropriate identification and wording choices were followed according to the GRADE working group [27]. A "Good practice statement" represents a message perceived by the guideline panel as necessary to health care practice, that is supported by a large body of indirect evidence difficult to summarize, and indicates that implementing this recommendation would clearly result in large net positive consequences. For recommendations where the comparators are not formally stated, the comparison of interest was implicitly referred to as "not using the test". Some recommendations acknowledge the current "knowledge gap" and aim at avoiding premature favorable recommendations for test use and to avoid encouraging the rapid diffusion of potentially inaccurate tests. Detailed suggestions about the specific research questions that should be addressed are found in **Table 2**.

Figure 2. 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)

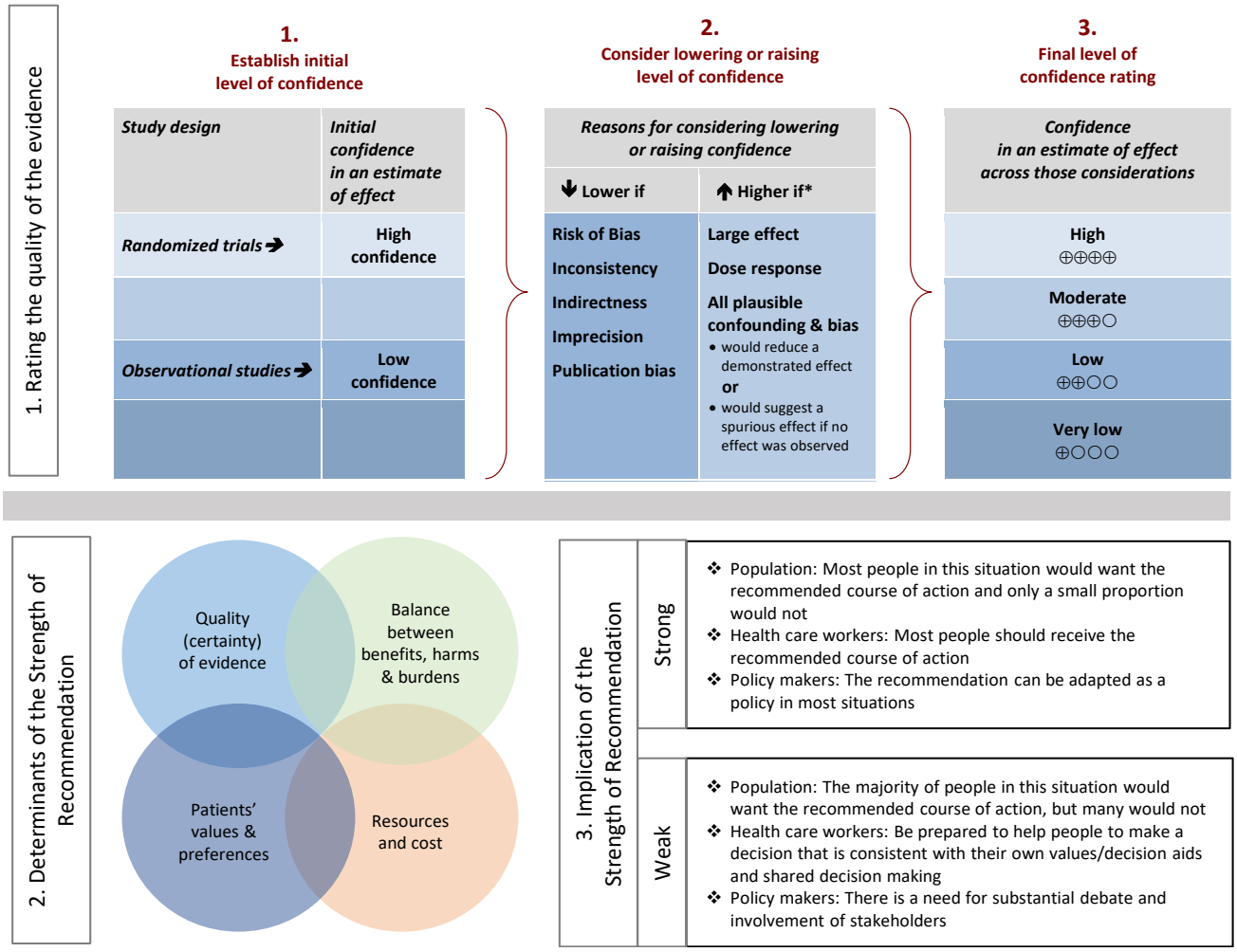


Table 2. Suggested Diagnostic Studies

	Diagnostic Research Needs Addressing Symptomatic Patients	**Diagnostic Research Needs Addressing Asymptomatic Individuals Known to Have Been Exposed to a Laboratory-Confirmed COVID-19 Case**
Research Needs	1. Measurements of clinical test performance (assay sensitivity and specificity) 2. Specimen type and/or collection methods comparisons	1. Measurements of clinical test performance (assay sensitivity and specificity) 2. Percent test positive 3. Specimen type comparisons 4. Post-exposure outcomes including timing of positive test results after exposure
Study Design	• Prospective observational cohort, either cross-sectional or longitudinal • A priori defined diagnostic reference standard • Same specimen type(s)/methods collected from all enrolled subjects	• Prospective observational, longitudinal cohort • A priori defined diagnostic reference standard • Same specimen type(s)/methods collected from all enrolled subjects over time
Subjects	Symptomatic patients suspected to have COVID-19 stratified by URI, ILI and/or LRTI	Asymptomatic individuals known to have been exposed to a COVID-19 case
Required Clinical Information	• Symptomatic patients suspected to have COVID-19 stratified by URI, ILI and/or LRTI	• Exposure assessment • Details of specimen collection • Timing of specimen collection relative to last exposure

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 by ASM, SHEA and PIDS, and endorsed by ASM and PIDS. The IDSA Board of Directors Executive Committee reviewed and approved the guideline prior to dissemination.

Updating Process

Regular, frequent screening of the literature will take place to determine the need for revisions based on the likelihood that new data will have an impact on the recommendations. If necessary, the expert panel will be reconvened to discuss potential changes. In addition, future searches will include critical appraisal of the SARS-CoV-2 serology literature.

Results

Systematic review and horizon scan of the literature identified 2,909 references of which 23 informed the evidence base for these recommendations (**Figure s1**). Characteristics of the included studies can be found in **Table s4**. Figure 1 summarizes a testing algorithm for COVID-19 diagnosis guidelines.

Recommendation 1. The IDSA panel recommends a SARS-CoV-2 nucleic acid amplification test (NAAT) in symptomatic individuals in the community suspected of having COVID-19, even when the clinical suspicion for COVID-19 is low (strong recommendation, very low certainty of evidence).

Remarks:

- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (Table 1).
- Clinical assessment alone is not accurate in predicting COVID-19 diagnosis.
- The panel considered timeliness of SARS-CoV-2 NAAT results essential to impact individual care, healthcare institution, and public health decisions. In the outpatient setting, results within 48 hours of collection is preferable.

Summary of the evidence: Direct evidence comparing the effects of NAAT testing *versus* no testing in symptomatic individuals in the community suspected of having COVID-19 was lacking. We identified eight studies that provided indirect information about rates of false positive

results in populations identified as potentially having COVID-19 based on various clinical symptoms and signs [8-12, 28-30] (**Table s5**). Clinical diagnostic scenarios were variable and included respiratory symptoms such as cough, shortness of breath, fever, alongside radiologic and biomarker indicators of having the disease. These studies included hospitalized and non-hospitalized patients. Four of the studies included in the analysis involved patients presenting to the hospital, potentially with pneumonia, which is different from a community-based symptomatic population [10, 11, 29, 30]. Due the mentioned concerns with the studies and the inconsistency among them, the panel assessed the overall certainty of evidence as very low.

Benefits and harms: The panel considered minimizing the number of the false positive COVID-19 diagnoses to be a priority. Relying solely on clinical judgment to make a diagnosis of COVID-19 led to a large proportion of patients being diagnosed with COVID-19 when they did not have the disease (over diagnosis ranged between 62 and 98%). Even in hospitalized patients with pneumonia, the proportion of false positive diagnoses reached 62% in some studies. The harmful consequences of over diagnosis (i.e., false positive results) are unnecessary isolation/quarantine and possible exposure to treatment. Additionally, people may believe incorrectly that they have already been infected with SARS-CoV-2 and stop taking the appropriate precautions which could lead to additional harms of further spreading the disease in the future. Based on the available evidence, and despite its limitations, there is high certainty that testing will decrease the number of false positives considerably. The panel considered this as a critical benefit of using testing compared to no testing. One can speculate that considering the high proportion of asymptomatic individuals who have the disease, relying solely on clinical presentation is likely to also lead to a high number of false negatives. The panel also considered false negatives to be a potential harm of testing. False negative test results could cause symptomatic individuals to ignore isolation/quarantine directives. Unfortunately, data was completely lacking to directly assess the rates of false negatives in the included studies.

Additional considerations: SARS-CoV-2 testing is acceptable to patients and providers. However, testing is not widely available in some areas.

Conclusions and research needs for this recommendation: SARS-CoV-2 testing is recommended for all symptomatic patients in the community. However, the availability of test reagents, specimen collection devices, and PPE shortages may influence who can realistically be tested. When resources are limited, prioritizing testing to high-risk groups may be necessary. The CDC, IDSA, and other agencies have published priorities for testing patients with suspected COVID-19 infection [31, 32]. Future studies are needed to assess the frequency of false negative NAAT results in community-based settings, where patients are more likely to present with mild or moderate symptoms.

Recommendation 2: The IDSA panel suggests collecting nasopharyngeal, or mid-turbinate or nasal swabs rather than oropharyngeal swabs or saliva alone for SARS-CoV-2 RNA testing in symptomatic individuals with upper respiratory tract infection (URTI) or influenza like illness (ILI) suspected of having COVID-19 (conditional recommendation, very low certainty of evidence).

Remarks:

- This recommendation does not address testing a combination of specimen types due to lack of evidence.
- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Summary of evidence: Thirteen studies informed this recommendation [33-45] and they provided varying descriptions of specimen type (**Supplement C**). In an effort to maintain consistency in the analysis of evidence, reported specimen types were grouped into nasopharyngeal (NP), mid-turbinate (MT), nasal, throat, or saliva. In studies that did not define collection techniques for "nasal", we assumed it to mean anterior nasal and not deep-nasal or nasopharyngeal. Saliva collection methods were also inconsistent. Saliva studies incorporating a "coughed-up" sample were excluded from the URTI and ILI analysis under the assumption that they likely included some mixture of pure saliva and sputum. Analyses of "tongue" swabs were

also excluded. It is important to note as well, that not all specimens were collected from the same patient at the same time, the time of collection from symptom onset was not provided in all studies and various approaches for establishing SARS-CoV-2 positivity were used to define positive results (i.e., clinical evaluation, detection different gene targets *versus* nucleic acid sequencing).

A total of 11 reports presented data about test accuracy of a specific sample type(s); eight of these [35, 36, 38-41, 43, 44] provided comparative data for two or more sample collection sites; and three others [33, 37, 45] provided data for one site only. Studies with comparative data showed a lower sensitivity for oral sampling in comparison to NP, MT, or nasal sampling. Summary statistics different specimen type are shown in **Table 3**. Two studies [38, 39] directly compared detection by nasal swab against NP swab as the reference method, showing the sensitivity of nasal to be comparable to NP sampling. Of note, the Tu et al. [39] study compared self-collected "mid-nasal" and nasal sampling and Peres et al. evaluated healthcare-collected "mid-nasal" sampling. Two additional studies provided indirect evidence without diagnostic test accuracy data. Osterdahl M. et al. [34] showed that three patients with negative throat samples taken on day 3 after symptom onset, had a positive result on throat samples taken on day 4 after symptoms onset. Zou L. et al, (2020) [42] observed higher amounts of viral RNA in nose compared to the throat swabs. We identified a single study [41] evaluating pure saliva sampling in comparison to NP swabbing; it showed saliva had 85% (95% CI (69%-94%) sensitivity with a lower viral load inferred from the PCR crossing threshold. Due the mentioned concerns with these studies, indirect comparisons between different sampling types and the inconsistency among them, the panel agreed that the overall certainty of evidence was very low.

Benefits and harms: NP swabs have long been considered the upper respiratory tract (URT) specimen of choice for respiratory virus NAAT. The potential harms of alternative URT specimen types are false negative results, which could promote unchecked SARS-CoV-2 transmission. One potential benefit of the alternative methods are the less-invasive nature of nasal, MT and throat swabs or saliva as compared to NP sampling. In addition, the PPE requirements for

healthcare providers collecting non-cough inducing specimen types may be less. Lastly, the non-NP sampling is amendable to patient self-collection, which has the potential to further reduce healthcare worker exposure to infectious droplets and possible droplet nuclei.

Additional considerations: Indirect evidence from influenza and respiratory syncytial virus studies suggest that alternative nasal cavity collection sampling methods such as anterior nasal and MT swabs provide comparable sensitivity to NP swabs [46]. Using NP swab collection as the reference method will bias evaluation of the comparator method by definition. Saliva is an easily obtained specimen and there is significant recent interest in its use for SARS-CoV-2 detection. At the time of this literature review we identified a single study assessing true saliva as a specimen type. This is a promising specimen type given the simplicity of collection. The panel anticipates multiple additional studies to follow, which will be included in future guideline updates. The panel considered indirect evidence for nasal swabs and MT swabs from other respiratory viruses in the decision to list these specimen types are preferred over saliva. In addition, saliva is complex matrix and clinical laboratories will need to carefully assess RNA stability during specimen transport and the efficiency of nucleic acid extraction using their own specific methods. We did not identify any studies assessing combinations of specimen types.

Conclusions and research needs for this recommendation: Although oropharyngeal swabs or saliva can be utilized for the diagnosis of COVID-19, the available evidence combined with indirect evidence from other respiratory viruses suggests that collection of anterior nares, MT, or NP swabs has higher sensitivity. At the current time, there is little evidence to support use of oropharyngeal swabs or saliva alone. However, future studies of saliva as a specimen type for SARS-Co-2 detection are anticipated.

Evaluation of alternative collection devices and methods are critically needed as we are facing shortages in test collection supplies such as swabs, transport media and PPE. While NP swab collection is widely used and the primary specimen type for commercial direct SARS-CoV-2 test platforms, based on current available evidence, clinical practice, and availability of testing

resources, the panel believes there are comparable alternative methods for sampling the nasal passages. Clinical laboratories will need to validate use of individual specimen types. Future studies of saliva should clearly describe collection methods, specimen transport media and processing requirements. Moving forward, it will be critical to standardize these processes.

Table 3. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 10% for different specimen types

	Oral	Nasal	Nasopharyngeal (NP)	Nasal (2 studies NP as comparator)	Saliva	Mid-turbinate
Sensitivity %(95% CI)	56 (35 to 77)	76 (59 to94)	97 (92 to 100)	95 (87 to 100)	85 (69 to 94)	100 (93 to 100)
Specificity %(95% CI)	99 (99 to 100)	100 (99 to 100)	100 (99 to 100)	100 (99 to 100)	100 (99 to 100)	100 (99 to 100)

Outcome	Effect per 1,000 patients tested						№ of patients (studies)	Test accuracy CoE [f]
	pre-test probability of 10% [e]							
	Oral	Nasal	Nasopharyngeal	Nasal (2 studies)	Saliva	MT		
True positives (patients with COVID-19)	56 (35 to 77)	76 (59 to 94)	97 (92 to 100)	95 (87 to 100)	85 (69 to 94)	100 (93 to 100)	Oral: 645 (4) Nasal: 412 (7) NP: 185 (4) Nasal (2 studies): 85 (2) Saliva: 39 (1) MT: 50 (1)	⊕◯◯◯ VERY LOW [a,b,c,d]
False negatives (patients incorrectly classified as not having COVID-19)	44 (23 to 65)	24 (6 to 41)	3(0 to 8)	5 (0 to 13)	15 (6 to 31)	0 (0 to 7)		
True negatives (patients without COVID-19)	891 (891 to 900)	900 (891 to 900)	900 (891 to 900)	900 (891 to 900)	882 (684 to 900	900 (882 to 900)	Nasal 457 (2) Saliva: 489 (1) MT: 452 (1)*	⊕◯◯◯ VERY LOW [a,b,c,d]
False positives (patients incorrectly classified as having COVID-19)	9 (0 to 9)	0 (0 to 9)	0 (0 to 9)	0 (0 to 9)	18 (0 to 216)	0 (0 to 18)		

Explanations: This table is based on applying the sensitivity and specificity estimates to calculate True and false positives and negatives in a hypothetical population of 1000 individuals.

*No studies reported on the specificity of oral and NP
a. The case-control design leads to a serious study population bias.
b. Some studies compared two or more of the specimen types, but no studies compared all specimen types in the same patient population. Studies reported test accuracy results but did not report on patient-important and population-important outcomes based on the results.
c. There is serious unexplained heterogeneity.
d. Considering the upper vs lower limits of the sensitivity's confidence interval would lead to different clinical decisions.
e. Typically seen in symptomatic outpatients who have not reached a hospital facility.
f. Certainty of evidence (CoE)

Recommendation 3. The IDSA panel suggests that nasal and mid-turbinate (MT) swab specimens may be collected for SARS-CoV-2 RNA testing by either patients or healthcare providers, in symptomatic individuals with upper respiratory tract infection (URTI) or influenza like illness (ILI) suspected of having COVID-19 (conditional recommendation, low certainty of evidence).

Remarks:

- Appropriate specimen collection and transport to the laboratory is critical. General instructions for swab-based SARS-CoV2 testing are shown in **Table 4**. Additional resources are available on the IDSA website.
- A clear, step-by-step protocol needs to be presented to patients attempting self-collection. This could be in the form of a short video or printed pamphlet with illustrations.
- The majority of self-collection studies were performed in the presence of a healthcare worker.
- The available evidence for nasal and MT swabs as alternatives to healthcare personnel collection is based on assessment of symptomatic patients. Data on self-collection in asymptomatic individuals is currently unavailable.
- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Summary of the evidence: This recommendation is based on three cohort studies (**Supplement D**). In the first study, test accuracy results were provided for self-collected non-invasive

specimens compared to healthcare-collected NP swabs as the standard [39]. For self-collection, participants were provided with instructions and asked to self-collect tongue, nasal, and MT swabs, in that order. Tongue samples were collected with a nylon flocked swab. Nasal samples were collected with a foam swab bilaterally. Mid-turbinate samples were collected with a nylon flocked swab bilaterally. After patient sampling was completed, NP samples were collected by a healthcare worker using a polyester tipped swab on a skinny wire. In the second study, patients attending dedicated COVID-19 collection clinics were offered the option to first self-collect nasal and throat swabs followed by healthcare provider collection of nasal, throat or oropharyngeal swabs [44]; concordance of results were presented. The third study compared positivity for supervised oral fluid sampling, supervised self-collected deep nasal swabs, unsupervised oral fluid sampling and provider collected NP swabs [43]. In this analysis, any positive test, obtained from any of the reported sampling methods including the index test, was considered to be a true positive. Although the study reported the results for "oral fluid", it is likely these samples were mixed with sputum. Lastly, the panel considered unpublished data submitted to the FDA on home collection, which demonstrated good stability of specimens stored in universal transport media (UTM) during transport from homes to laboratories and comparable quantities of virus in self-collected compared to healthcare provider collected swabs. Summary statistics for self-collected versus health-care worker collected nasal swabs are shown in **Table 5**.

The studies used to inform the recommendation were small and heterogeneous. Sources of heterogeneity included variable swab and transport media types as well as use of unilateral *versus* bilateral nares self-collection. The timing of collection relative to symptom onset is also important but was not well documented in available data. Due to the mentioned concerns with the studies and the lack of direct comparisons between different specimen types in the same patient population, the panel agreed that overall certainty of evidence was low.

Benefits and harms: The panel placed a high value on avoiding the close exposure of healthcare providers to patient droplets and possible droplet nuclei generated during specimen collection.

We assumed that self-collected specimens including anterior nasal swabs, MT swabs and saliva (without cough) would reduce provider exposure and could reduce mask or respirator use. The overall sensitivity of testing when samples were collected by patients was comparable to those collected by healthcare providers.

Additional considerations: Other potential benefits of self-collection include increasing the availability of testing outside the healthcare system and increased patient satisfaction with self-collection. Concerns with self-collection include lack of experience or documentation for actual collection methods by patients; inappropriate sample collection and/or handling could then lead to inaccurate results.

Conclusions and research needs for this recommendation: Although data is limited, both healthcare provider collected, and self-collected nasal or MT swabs appear to result in similar rates of detection of SARS-CoV-2. Self-collection of NP swabs is unlikely to be an option as a self-collection method. There are advantages of having multiple strategies to collect clinical specimens, particularly in times of PPE shortages when limiting exposure to healthcare personnel or other patients is important, or when testing in specific populations without access to the healthcare system is required. Further comparative studies of self-collected non-invasive specimens (i.e., nasal, mid-turbinate, and throat swabs, as well as saliva) compared with healthcare provider-collected NP swabs is warranted. Research is needed comparing sample collection at various intervals from time of onset of symptoms, evaluation of single *versus* two-sided sampling, and quantitation of virus recovery from samples obtained via different collection methods. Studies comparing collection methods in symptomatic and asymptomatic individuals are also needed. Lastly, studies of home-collection in asymptomatic individuals and parental swab collection in children with COVID-19 are needed.

Table 4. General Instructions for Swab-based SARS-CoV2 Testing

	Nasopharyngeal*	Oropharyngeal	Mid-Turbinate	Nasal/Anterior Nares
Who Collects	Healthcare professional	• Healthcare professional • Medical-supervised on-site self-collection	• Healthcare professional • Medical-supervised on-site self-collection	• Healthcare professional • Medical-supervised on-site self-collection
Tools/ Equipment^	Flocked, synthetic fiber mini-tip swabs with plastic or wire shafts	Synthetic fiber swabs with plastic shafts only	Flocked tapered swab	Flocked, synthetic fiber or foam swab with plastic shaft
How to Collect	1. Tilt patient's head back 70° 2. Insert flexible shaft mini-tip swab through nares parallel to palate (not upwards) until: a. Resistance is met, **OR** b. Distance is equivalent to the distance from the patient's ear to their nostril 3. Gently rub and roll swab 4. Leave swab in place for several seconds to absorb secretions 5. Slowly remove swab while rotating it 6. Immediately place swab in sterile tubes containing transport media If collected with OP, combine in single tube → limit use of testing resources	1. Insert swab in posterior pharynx and tonsillar areas 2. Rub swab over posterior pharynx and bilateral tonsillar pillars; avoid tongue, teeth, and gums 3. Immediately place swab in sterile tubes containing transport media If collected with NP, combine in single tube → limit use of testing resources	1. Tilt patient's head back 70° 2. While gently rotating swab, insert swab about 2.5 cm (≥1 in.)[#] straight back (not up) into nostril until the collar/safety stopping point touches the outside of the nose 3. Rotate swab several times against wall 4. Leave swab in place for several seconds to absorb secretions 5. Repeat for both nostrils using same swab[#] 6. Immediately place in sterile tube containing transport media	1. Insert swab about 1 cm (0.5 in) inside nares[#] 2. Rotate swab and leave in place for 10-15 seconds 3. Using same swab, repeat for other nostril 4. Immediately place in sterile tube containing transport media

Sources:
Centers for Disease Control and Prevention. Guidelines for Clinical Specimens. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html. Accessed 22 April 2020.

Food and Drug Administration. Specimen Collection FAQs. Available at: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2. Accessed 29 April 2020.

Abbreviations: NP = nasopharyngeal; OP = oropharyngeal; MT = nasal mid-turbinate; NS = anterior nares swab.

^**Cautions:** Do NOT use calcium alginate swabs or swabs with wooden shafts, which may contain substances that interfere with nucleic acid amplification. Rayon swabs may not be compatible with all molecular platforms. Clinical laboratories should confirm compatibility of collection devices during assay validation.

#**Pediatrics**: Swab insertion distance will differ for pediatric patients. Swabs with stoppers make estimating distance easier for MT self-collection. Two-sided MT sampling not always performed.

Table 5. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 10% for Self-Collected versus Healthcare Collected samples

Self-collected nasal	**Sensitivity: 0.95 (95% CI: 0.88 to 1.00) Specificity: 1.00 (95% CI: 0.99 to 1.00)**			
Health care worker collected	**Sensitivity: 0.94 (95% CI: 0.86 to 1.00) Specificity: 1.00 (95% CI: 0.99 to 1.00)**			
Outcome	**Effect per 1,000 patients tested**		**№ of patients (studies)**	**Test accuracy CoE [d]**
	pre-test probability of 10% [c]			
	Self-collected nasal	Health care worker collected		
True positives (patients with COVID-19)	95 (88 to 100)	94 (86 to 100)	200 (3)	⊕⊕◯◯ LOW [a,b]
	1 more TP in Self-collected Nasal			
False negatives (patients incorrectly classified as not having COVID-19)	5 (0 to 12)	6 (0 to 14)		
	1 fewer FN in Self-collected Nasal			
True negatives (patients without COVID-19)	900 (891 to 900)	900 (891 to 900)	600 (3)	⊕⊕◯◯ LOW [a,b]
	0 fewer TN in Self-collected Nasal			
False positives (patients incorrectly classified as having COVID-19)	0 (0 to 9)	0 (0 to 9)		
	0 fewer FP in Self-collected Nasal			

Explanations: This table is based on applying the sensitivity and specificity estimates to calculate True and false positives and negatives in a hypothetical population of 1000 individuals

a. There is a high risk of bias in regard to the reference test that is considered to be the healthcare provider collected swab result.
b. The studies provide test accuracy results or concordance results but do not provide patient-important outcomes based on those results.
c. Typically seen in symptomatic outpatients who have not reached a hospital facility
d. Certainty of evidence (CoE)

Recommendation 4: The IDSA panel suggests a strategy of initially obtaining an upper respiratory tract sample (e.g., nasopharyngeal swab) rather than a lower respiratory sample for SARS-CoV-2 RNA testing in hospitalized patients with suspected COVID-19 lower respiratory tract infection. If the initial upper respiratory sample result is negative, and the suspicion for disease remains high, the IDSA panel suggests collecting a lower respiratory tract sample (e.g., sputum, bronchoalveolar lavage fluid, tracheal aspirate) rather than collecting another upper respiratory sample (conditional recommendations, very low certainty of evidence).

Remark: The panel considered timeliness of SARS-CoV-2 NAAT results essential to impact individual care and isolation decisions. In the hospital setting, results within 24 hours of collection is preferable.

Summary of the Evidence: We identified nine studies that performed both an upper respiratory tract (URT) swab and lower respiratory tract (LRT) sample collection consecutively on the same patient (**Supplement E**). Two reported on viral load and did not report on sensitivity [47, 48]. Seven studies reported on sensitivity, of which three had a case control design [35, 49, 50] and one reported results per sample and not per patient [51]. The three cohort studies [43, 52, 53] were used to inform the panel's decision-making process. The sample type varied by study and included throat and nasal swabs for URT sampling and sputum and bronchoalveolar lavage (BAL) fluid specimens for LRT sampling. Summary statistics for URT versus LRT sampling in 3 cohort studies are shown in **Table 6**. The timing of specimen collection with regards to clinical course was not reported for all these studies and different diagnostic reference standards were

used. These issues led to very low certainty about test accuracy results comparing URT *versus* LRT samples.

Benefits and harms: The evidence suggests that testing LRT specimens increases sensitivity of testing for SARS-CoV-2 RNA, reducing the number of false negative results. The panel considered minimizing the number of false negatives to be the most important priority when analyzing the data. This approach was taken to strengthen both the individual and population impact of the tests evaluated. The obvious benefit of LRT testing is to reduce the numbers of patients whose infection is missed and pose a risk to others. There are also risks to collecting LRT samples in infected patients, including the possibility of aerosolization and increased PPE requirement, which may be in short supply.

Additional considerations: It was assumed that patients fulfilling clinical criteria for COVID-19 pneumonia, in a hospital setting, would exhibit a high or very high likelihood of true infection. The use of a LRT sample would therefore only apply to patients ill enough to be hospitalized including those likely to be in intensive care units. The panel also considered the feasibility concerns with suggesting lower sampling for all patients with signs/symptoms of lower respiratory tract infection (LRTI). These included that not all patients may be able to produce sputum, PPE shortages may impact the availability of more invasive sampling, and not all laboratories may have validated testing using LRT samples. The panel agreed that a tracheal aspirate, as opposed to BAL, may be the most feasible specimen in intubated patients. In some situations, obtaining a lower sample first may be easier such that an NP sample is not required. Induced sputum should be avoided due to risk for aerosol generation. Regardless of the LRT sample used, assay validation for these specimen types might remain an issue. Additionally, it is important to note that confirmation of infection is also typically required for enrollment in clinical trials of investigational agents.

Conclusions and research needs for this recommendation: Considering the upper and lower limits of the confidence intervals in the sensitivity value, the panel believes the increased

sensitivity of the LRT sample would lead to more appropriate clinical and infection control decisions. However, feasibility concerns with LRT sampling prompted the panel to suggest a diagnostic strategy that incorporated both upper and lower sampling to minimize the amount of lower sampling needed. Large (multicenter) comparative studies are needed to assess the accuracy of upper and lower respiratory tract samples collected from the same patient for the diagnosis of COVID-19 pneumonia. Simultaneous collection of NP swabs and sputum are of particular interest. Studies should include assessment of the timing of specimen collection in relationship to the onset of symptoms and use widely available, validated tests in combination with a standardized definition of COVID-19 LRTI.

Table 6. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 40% and 80% for upper respiratory tract (URT) vs lower respiratory tract (LRT) Sampling (3 studies)

URT sampling	**Sensitivity: 0.76 (95% CI: 0.51 to 1.00 Specificity: 1.00 (95% CI: 0.99 to 1.00)**					
LRT sampling	**Sensitivity: 0.89 (95% CI: 0.84 to 0.94) Specificity: 1.00 (95% CI: 0.99 to 1.00)**					
Outcome	**Effect per 1,000 patients tested**				**No patients (studies)**	**Test accuracy CoE** [f]
	pre-test probability of 40% [d]		pre-test probability of 80% [e]			
	URT sampling	LRT sampling	URT sampling	LRT sampling		
True positives (patients with COVID-19)	304 (204 to 400)	356 (336 to 376)	608 (408 to 800)	712 (672 to 752)	280 (3)	⊕◯◯◯ VERY LOW [a,b,c]
	52 fewer TP in URT sampling		**104 fewer TP in URT sampling**			
False negatives (patients incorrectly classified as not having COVID-19)	96 (0 to 196)	44 (24 to 64)	192 (0 to 392)	88 (48 to 128)		
	52 more FN in URT sampling		**104 more FN in URT sampling**			
True negatives (patients without COVID-19)	600 (594 to 600)	600 (594 to 600)	200 (198 to 200)	200 (198 to 200)	8 (1)	⊕◯◯◯ VERY LOW [a,c]
	0 fewer TN in URT sampling		**0 fewer TN in URT sampling**			
False positives (patients incorrectly classified as having COVID-19)	0 (0 to 6)	0 (0 to 6)	0 (0 to 2)	0 (0 to 2)		
	0 fewer FP in URT sampling		**0 fewer FP in URT sampling**			

Explanations: This table is based on applying the sensitivity and specificity estimates to calculate True and false positives and negatives in a hypothetical population of 1000 individuals

a. There was no direct evidence comparing the accuracy of a strategy with starting with upper sample and then conducting a lower sample if the upper sample is negative. Additionally, studies reported test accuracy results but did not report on patient-important and population-important outcomes based on the results.

b. There is serious unexplained heterogeneity.

c. Considering the upper vs lower limits of the sensitivity's confidence interval would lead to different clinical decisions. Also, only one study informed specificity with only 8 patients.

d. Typically seen in patients meeting clinical definition for COVID-19 who were hospitalized.

e. Typically seen in patients meeting clinical definition for COVID-19 who were admitted to intensive care units.

f. Certainty of evidence (CoE)

Recommendation 5: The IDSA panel suggests performing a single viral RNA test and not repeating testing in symptomatic individuals with a low clinical suspicion of COVID-19 (conditional recommendation, low certainty of evidence).

Remarks:

- A low clinical suspicion should be informed by epidemiological information available for the region coupled with clinical judgment.
- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Recommendation 6: The IDSA panel suggests repeating viral RNA testing when the initial test is negative (*versus* performing a single test) in symptomatic individuals with an intermediate or high clinical suspicion of COVID-19 (conditional recommendation, low certainty of evidence).

Remarks:

- Intermediate/high clinical suspicion typically applies to the hospital setting and is based on the severity, numbers and timing of compatible clinical signs/symptoms.
- Repeat testing should generally occur 24-48 hours after initial testing and once the initial NAAT result has returned as negative.
- Another specimen type, preferably a lower respiratory tract specimen if the patient has signs/symptoms of LRTI, should be considered for repeat testing.
- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Summary of the evidence: These recommendations are based on a three cohort studies [11, 54, 55] (**Supplement F**). In these reports, targeted NAAT testing was performed using a NP swab collected from symptomatic patients with signs of LRTI. The diagnostic reference standard was detection of SARS-CoV-2 by metagenomics sequencing. If the first NAAT result was negative, a second NP sample was collected 2 or 3 days later for repeat testing. Summary statistics for

single versus repeated testing are shown in **Table 7**. We did not identify any studies that assessed the benefits and harms of repeat testing on patient or population outcomes. Given the lack of direct assessment of the implications of single *versus* repeat testing and the small number of patients included in the identified studies, the panel agreed that the overall certainty of evidence was low.

Benefits and harms: The panel placed a high value on avoiding a missed diagnosis in patients who have COVID-19 (i.e., false negatives) in the inpatient setting. Patients who are inappropriately labeled as not having COVID-19 pose a risk of transmitting the virus to others in the community, to healthcare providers and staff as well as other patients in the hospital. The panel determined that a false negative (FN) rate of <2% would be acceptable. Single testing compared to repeat testing will lead to a FN rate of about 10-20 cases out of 1000 in the low clinical suspicion group and to higher rates (FN of >60 cases out of 1000) in the intermediate and high clinical suspicion groups.

Additional considerations: Multiple factors affect the generalizability of available evidence for or against repeat testing. First, the selected studies included subjects with a high likelihood of COVID-19 based on epidemiology and clinical symptoms. Consideration of disease prevalence is important given that the negative predictive value (NPV) of a diagnostic test increases as the disease prevalence decreases. Thus, a single negative COVID-19 test result in areas of low disease prevalence is more predictive than in areas of high disease prevalence. We also assumed that the performance of the assays studied was comparable to commercial NAAT platforms currently available in the United States. Other studies evaluating repeat testing have utilized different gold standards, such as chest CT findings, and relied on throat swabs, which may not be as sensitive as NP specimens. In addition, the diagnostic yield of a second test may be impacted by the duration of symptoms and the clinical site sampled. Depending on the clinical situation (e.g., whether pneumonia is present or not) and disease progression, alternative specimen types such as a lower respiratory collection should be considered. Evidence suggests that viral distribution in different anatomical sites can impact detection and

virus loads may be higher in lower respiratory tract symptoms. Clinicians are advised to contact their local laboratory to determine locally acceptable specimen types for SARS-CoV-2 RNA testing.

Conclusions and research needs for this recommendation: High-quality evidence addressing the predictive value of a single negative SARS-CoV-2 test result compared to repeat testing for clinical diagnosis is lacking. Based on current available evidence, clinical practice, and availability of testing resources, the panel recommends use of clinical judgment combined with knowledge of local epidemiology in considering repeat molecular testing of respiratory tract samples. In settings with lower rates of SARS-CoV-2 circulation in the community, or in persons with symptoms not typical of COVID-19, benefits of repeat testing may be lower. When repeat testing is warranted, the site of specimen collection should be carefully assessed. Further studies evaluating the potential benefit and timing of repeat testing relative to symptom onset in both inpatient and outpatient settings are warranted.

Table 7. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 10% and 40% for single versus repeat PCR testing

Single testing	**Sensitivity: 0.71 (95% CI: 0.65 to 0.77)** **Specificity: 1.00 (95% CI: 0.99 to 1.00)**					
Repeat testing	**Sensitivity: 0.88 (95% CI: 0.80 to 0.96)** **Specificity: 1.00 (95% CI: 0.99 to 1.00)**					
Outcome	**Effect per 1,000 patients tested**				**№ of patients (studies)**	**Test accuracy CoE[e]**
	pre-test probability of 10% [c]		**pre-test probability of 40% [d]**			
	RT-PCR Single testing	RT-PCR Repeat testing	RT-PCR single testing	RT-PCR Repeat testing		
True positives (TP) (patients with COVID 19)	71 (65 to 77)	88 (80 to 96)	284 (260 to 308)	352 (320 to 384)	253 (3)	⨁⨁◯◯ LOW [a,b]
	17 fewer TP in RT-PCR rapid testing		**68 fewer TP in RT-PCR rapid testing**			
False negatives (FN) (patients incorrectly classified as not having COVID 19)	29 (23 to 35)	12 (4 to 20)	116 (92 to 140)	48 (16 to 80)		
	17 more FN in RT-PCR rapid testing		**68 more FN in RT-PCR rapid testing**			
True negatives (TN) (patients without COVID 19)	900 (891 to 900)	900 (891 to 900)	600 (594 to 600)	600 (594 to 600)	105 (2)	⨁⨁◯◯ LOW [a,b]
	0 fewer TN in RT-PCR rapid testing		**0 fewer TN in RT-PCR rapid testing**			
False positives (FP) (patients incorrectly classified as having COVID 19)	0 (0 to 9)	0 (0 to 9)	0 (0 to 6)	0 (0 to 6)		
	0 fewer FP in RT-PCR rapid testing		**0 fewer FP in RT-PCR rapid testing**			

Explanations: This table is based on applying the sensitivity and specificity estimates to calculate True and false positives and negatives in a hypothetical population of 1000 individuals

a. Studies reported test accuracy results but did not report on patient-important and population-important outcomes based on the results.

b. Considering the lower vs upper limit of the sensitivity confidence interval may lead to different clinical decision, and the low number of patients lead to very serious imprecision

c. Typically seen in symptomatic outpatients who have not reached a hospital facility

d. Typically seen in patients meeting clinical definition for COVID-19 who were hospitalized

e. Certainty of evidence (CoE)

Recommendation 7: The IDSA panel makes no recommendations for or against using rapid (i.e., test time ≤ 1hour) versus standard RNA testing in symptomatic individuals suspected of having COVID-19 (knowledge gap).

Evidence summary: We identified seven studies describing the use of a rapid NAAT [34, 56-59], with only two reporting on EUA tests [60, 61] (**Supplement G**). The sensitivity and specificity of the rapid isothermal EUA compared to standard laboratory-based assays ranged between 75-94% and 99-100%, respectively.

The overall body of evidence was limited by small numbers of infected patients, poorly defined reference standards, and studies based on numbers of samples in different patient groups rather than comparisons in the same patients. None of the available studies compared the two testing techniques (rapid *versus* standard) with a third diagnostic gold standard. In addition, multiple studies were case controlled which artificially inflates test accuracy [34, 56-59, 61]. Missing data in the studies included timing of specimen collection in relationship to onset of clinical symptoms and specimen type used for testing. Additionally, the performance and accuracy of different rapid tests was very inconsistent. Given all these issues, the overall certainty of the effect of using rapid tests on patients was very low.

Benefits and harms: The major benefit of a rapid result is the ability to make clinical decisions while the patient is present in a timely manner and implement interventions to protect others. A possible harm of rapid tests is the potential for increased numbers of false negative results, which could lead to missed diagnoses and patients not being isolated when they are indeed infected, if sensitivity is lower than non-rapid tests.

Additional considerations: Defining "rapid" NAAT requires consideration of several factors including time required to actually perform the test, the location of the testing facility (i.e., near the patient *versus* in a clinical laboratory and therefore how long it takes from specimen collection to initiation of testing), how often a particular test is performed by a laboratory and

whether tests are batched. For EUA approved tests, the time required to perform the test varies from as little as 15 minutes to several hours. There are CLIA-waived EUA tests that are very easy to use and can be performed by non-laboratory personal near patients and high complexity tests that must be performed by trained professionals in clinical laboratories. The laboratory-based tests are designed with either a batch format (combining many tests in a single run) or an on-demand format (running tests as they come into the laboratory). The turnaround time for on-demand tests should be faster than the batch approach, if there is adequate staffing in the laboratory to perform testing as specimens arrive in the laboratory, including day, evening and night shifts. Likewise, the turnaround time of batch tests can vary depending on whether the laboratory performs testing once per day versus once per shift, and whether the laboratory is open 24/7. Given these complexities, the panel defined a "rapid" test as one with a test time of an hour or less, with all others referred to as "standard" tests.

Most of the rapid tests evaluated in the identified studies used laboratory-developed reverse transcription-loop mediated isothermal amplification (RT-LAMP) technology. These RT-LAMP tests are not available for clinical use in the US and conversely none of the EUA approved rapid tests use RT-LAMP technology. There was no reason to believe that all rapid tests (whether EUA and non-EUA) had the same performance characteristics. Therefore, it was not possible to extrapolate data from a specific rapid test to all rapid tests. Recent studies have shown one rapid EUA test to be less sensitive than some laboratory-based tests [60, 61].

The quality of the available studies assessing rapid tests is poor, so it was not possible to make any meaningful recommendation on their use in clinical practice. If the rapid NAATs have equivalent performance to the standard NAATs, then there is potential to have results present in a time frame that impacts clinical decisions. If they are less sensitive than standard NAATs, then the benefit of the rapid NAATs needs to be weighed against the number of false negative results, which will lead to incorrect clinical decisions. It is unclear if the decreased accuracy of the rapid tests in the studies that were evaluated is due to performance characteristics of the test or other external factors such as specimen type (NP *versus* OP swabs), poor specimen

collection, testing directly from swabs versus from transport media (important for near patient testing) or timing of the collection of the specimen in relation to disease course.

Conclusions and research needs for this recommendation: Overall, there was inadequate information to compare the performance characteristics of the rapid and standard nucleic acid amplification tests in any symptomatic patient population, including outpatients and hospitalized patients. The panel does not recommend for or against rapid NAATs in symptomatic individuals suspected of having COVID-19 at this time due to the lack of quality evidence. More studies are needed to determine the appropriate role of rapid SARS-CoV-2 testing and the impact that rapid results have on clinical outcomes. Studies should be designed with a robust number of patients to define the clinical sensitivity and specificity of rapid and standard tests on the same patients. The same specimen would be used for both tests, but when this is not possible due to test design, sequentially collected specimens could be used. Diagnostic accuracy should be stratified by duration of symptoms and severity of disease. Furthermore, the diagnostic reference standard must be clearly defined. Performance characteristics of EUA rapid tests, especially those that are CLIA-waived, should be collected in the field and performed by the non-laboratory staff running the test (which is how they are used in real life). Ideally, studies should assess the impact of rapid results on clinical outcomes, such as time to appropriate treatment or therapeutic intervention.

Recommendation 8: The IDSA panel suggests SARS-CoV-2 RNA testing in asymptomatic individuals who are either known or suspected to have been exposed to COVID-19 (conditional recommendation, very low certainty of evidence).

Remarks:

- Known exposure was defined as direct contact with a laboratory confirmed case of COVID-19.
- Suspected exposure was defined as working or residing in a congregate setting (e.g., long-term care, correctional facility, cruise ship, factory, among others) experiencing a COVID-19 outbreak.

- The risk of contracting SARS-CoV-2 may vary under different exposure conditions.
- This recommendation assumes the exposed individual was not wearing appropriate PPE.
- The decision to test asymptomatic patients will be dependent on the availability of testing resources.

Summary of the evidence: We did not identify any studies that directly assessed a strategy of testing *versus* no testing of asymptomatic individuals exposed to SARS-CoV-2. Therefore, the effect of testing on the pre-specified outcomes could not be directly assessed. We also did not identify test accuracy studies directly assessing the performance of SARS-CoV-2 NAATs in asymptomatic individuals. However, based on evidence that asymptomatic or pre-symptomatic patients may have similar viral loads and shedding compared to those who are symptomatic [15, 62, 63], the panel agreed that it is reasonable to apply test accuracy data based on symptomatic patients to the asymptomatic populations. Hence, it was essential to determine the pre-test probability or prevalence of COVID-19 in the asymptomatic groups.

We assessed studies that reported the prevalence of COVID-19 among asymptomatic individuals in household clusters [15, 17, 19], a nursing home outbreak [14], active surveillance of passengers quarantined on a cruise ship or passengers of repatriation flights [18], hospital employees with close contact to COVID-19 positive patients [13], and customers and employees of a restaurant that had a COVID-19 outbreak [16]. Overall, prevalence ranged from 10 to 50% in settings where substantial transmission was suspected prior to testing. Summary statistics for single versus repeated testing are shown in **Table 8** and **Supplement H**. We acknowledge that information on individual exposure was limited in the evidence base. All these limitations led to very low certainty in the evidence overall.

Benefits and harms: Testing asymptomatic individuals who have been exposed, or suspected to have been exposed, allows for isolation for those who are positive. Whether in an institutional cluster or a wider community outbreak, isolation will help reduce further transmission. There is potential harm in a false negative NAAT result collected from an exposed individual who is

actually infected; these individuals may incorrectly consider themselves non-infected, and unknowingly expose others to SARS-CoV-2 as a result. Given the lack of evidence, a negative test post-exposure does not mean quarantine can be discontinued. Some individuals may still be in the incubation phase, subsequently develop active viral shedding, and incorrectly consider themselves non-infected. As a result, a negative post-exposure test cannot necessarily be used to avoid quarantine. A positive result, however, would reinforce the importance of isolation as well as inform contact tracing, cohorting, or other mitigation strategies.

Additional considerations: Diagnostic test performance in asymptomatic individuals has not been established. Assuming an overall test sensitivity between 75%-95% [35, 36, 38-40, 44], false negative test results are expected. There is also cost to testing asymptomatic exposed individuals; since quarantine may still be indicated regardless of test results, such testing may add cost without changing practice. Data are limited to define definitions of close contact. Risk stratification of a given exposure can be made in consultation with public health authorities. In addition, the CDC has published guidance on defining healthcare exposures and categorizing exposure risks [64].The ideal time to test an asymptomatic contact of a known or suspected COVID-19 case is also unknown. Timing also becomes complicated for household contacts with ongoing exposure. The average incubation period for SARS-CoV2 has been determined to be five days [65]. Thus, 5-7 days following exposure may be a reasonable time frame to consider post-exposure testing. In addition, data to inform the definition of a significant exposure or close contact are limited. Considerations when assessing the risk of a known contact include the duration of exposure and the clinical symptoms (e.g., cough) of the person with COVID-19.

Conclusions and research needs for this recommendation: Testing in asymptomatic subjects with known or suspected exposures should be coordinated with local public health officials. This indication for testing is especially important in situations where knowledge of asymptomatic or pre-symptomatic infection is essential for determining medical follow-up, defining risks for other vulnerable individuals in the household, congregate setting or hospital. Special consideration should also be given to healthcare personnel exposed without

appropriate PPE in healthcare settings. Definitions of appropriate PPE can be found on the CDC website [66].

Comparative studies (preferably randomized controlled trials) along with cost-effectiveness analyses of testing strategies in asymptomatic populations are needed. Studies on the ideal time and collection method to test asymptomatic individuals who have been exposed to COVID-19 should be performed. In addition, what constitutes an exposure that would justify testing requires further research. Whether early diagnosis of COVID-19 might provide an opportunity to intervene therapeutically and change the ultimate course of infection (i.e., prevent severe pneumonia) is unknown. If this is shown to be the case, the opportunity for therapeutic intervention might justify screening exposed individuals.

Table 8. GRADE Summary of Findings Table of Test Accuracy Results for Prevalence/Pre-Test Probability of 10% 25% and 50% for SARS CoV-2 PCR

Sensitivity	**0.75 (95% CI: 0.55 to 0.95)**				
Specificity	**0.99 (95% CI: 0.99 to 1.00)**				
Outcome	**Effect per 1,000 patients tested** [d]			**№ of patients (studies)**	**Test accuracy CoE** [e]
	pre-test probability of 10%	**pre-test probability of 25%**	**pre-test probability of 50%**		
True positives (patients with COVID-19)	**75** (55 to 95)	**188** (138 to 238)	**375** (275 to 475)	385 (6)	⊕◯◯◯ VERY LOW [a,b,c]
False negatives (patients incorrectly classified as not having COVID-19)	**25** (5 to 45)	**62** (12 to 112)	**125** (25 to 225)		
True negatives (patients without COVID-19)	900 (891 to 900)	750 (742 to 750)	500 (495 to 500)	457 (2)	⊕◯◯◯ VERY LOW [a,b,c]
False positives (patients incorrectly classified as having COVID-19)	0 (0 to 9)	0 (0 to 8)	0 (0 to 5)		

Explanations: This table is based on applying the sensitivity and specificity estimates to calculate True and false positives and negatives in a hypothetical population of 1000 individuals
a. Reference standard considered to be nasopharyngeal specimen RT-PCR.
b. Studies report test accuracy results but do not report on patient-important outcomes based on these results.
c. A small number of patients included.
d. We assessed studies that reported the prevalence of COVID-19 among asymptomatic individuals who were exposed to COVID-19 and determined that the prevalence may range from 10% to 50% based on household clusters, nursing home outbreak, active surveillance of passengers quarantined on a cruise ship or passengers of repatriation flights, hospital employees with close contact with COVID-19 positive patients and customers and employees of a restaurant that had a COVID-19 outbreak.
e. Certainty of evidence (CoE)

Recommendation 9: The IDSA panel suggests against SARS-CoV-2 RNA testing in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a low prevalence of COVID-19 in the community (conditional recommendation, very low certainty of evidence).

Remarks:

- Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19.
- A low prevalence of COVID-19 in the community was considered communities with a prevalence of <2%.
- This recommendation does not apply to immunocompromised individuals.
- This recommendation does not apply to individuals undergoing time-sensitive major surgery or aerosol generating procedures.

Recommendation 10: The IDSA panel recommends direct SARS-CoV-2 RNA testing in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a high prevalence of COVID-19 in the community (i.e., hotspots) (conditional recommendation, very low certainty of evidence).

Remarks:

- Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19.
- A high prevalence of COVID-19 in the community was considered communities with a prevalence of ≥10%.

- The decision to test asymptomatic patients (including when the prevalence is between 2 and 9%) will be dependent on the availability of testing resources.

Summary of evidence: We did not identify any studies that directly assessed a strategy of nucleic acid testing for SARS-CoV-2 *versus* no testing before hospitalization for non-COVID-19 related reasons. We also did not identify test accuracy studies directly assessing the performance of SARS-CoV-2 viral RNA tests in asymptomatic individuals. However, based on existing evidence suggesting that asymptomatic or pre-symptomatic patients may have similar virus loads and shedding as those who are symptomatic [62, 63], the panel agreed to infer test accuracy for asymptomatic populations before being hospitalized.

It was also essential to determine the pre-test probability or prevalence of the disease in asymptomatic patients admitted to the hospital. We assessed studies that reported prevalence of COVID-19 among asymptomatic individuals in the community and determined that the prevalence may range from <1 to 10% [8, 20, 21] (**Supplement I**). This range pertains to communities where there is low levels or high levels (i.e., "hot spots") of transmission of COVID-19. Significant limitations with the available evidence led to very low certainty in the effect of testing overall.

After considering consequences of missing a diagnosis of COVID-19 both on the individual- and population-level, and considering the sensitivity of the available tests, the panel determined that a maximum threshold of <10-20 missed cases per 1000 would be acceptable. Not testing individuals in low prevalence areas (<2%) met that threshold. However, in intermediate to high prevalence areas (>2%), not testing would lead to higher numbers of missed cases which the panel considered to exceed the acceptable threshold.

Benefits and harms: The panel considered the benefit of screening asymptomatic patients on admission to hospital in those areas where SARS-CoV-2 transmission is widespread ("hotspots"). The ability to identify positive patients and isolate them would help reduce the

risk of nosocomial outbreaks. However, there is potential harm in missing infected individuals (i.e., false negative NAAT results). False negatives could ultimately result in transmission to healthcare workers or other patients. Assuming an overall test sensitivity between 75% - 95% [35, 36, 38-40, 44], false negative test results are expected, and repeat testing may be necessary. Alternatively, false positive results would lead to unnecessary isolation, PPE usage and potentially cohorting with other positive patients.

Additional considerations: Determining the true prevalence of COVID-19 in the community is difficult and may be underestimated especially when test availability is limited. In addition, the panel's acceptable threshold for missed cases is expert opinion only and not based on cost-effectiveness data. There are costs and logistical challenges involved SARS-CoV-2 screening on admission. Ideally, test results should be available rapidly (i.e., results in an hour) to optimally inform bed management and need for isolation. However, not all hospitals may have access to rapid tests. In addition, when testing supplies are limited, prioritization of symptomatic patients may be required.

Conclusions and research needs for this recommendation: The panel's recommendations for testing asymptomatic patients on admission to the hospital do not address areas with intermediate prevalence (i.e., 2-9%). Individual institutions should base their testing strategies on available resources. Comparative studies (preferably randomized controlled trials) along with cost-effectiveness analyses of testing strategies in asymptomatic populations are needed. Well-designed point prevalence studies are also needed to better inform local and regional prevalence estimates. Shortages of PPE and/or testing for SARS-CoV-2 in some healthcare facilities may affect practicality of following the recommendation. Definitions as to what constitutes a hotspot or "high"-prevalence are needed. This recommendation may also need to be revisited over the course of the pandemic as rates of previously infected patients and healthcare workers, who may have protective immunity, change.

Recommendation 11: The IDSA panel recommends for SARS-CoV-2 RNA testing in immunocompromised asymptomatic individuals who are being admitted to the hospital regardless of exposure to COVID-19 (strong recommendation, very low certainty of evidence).

Remarks:

- This recommendation defines immunosuppressive procedures as cytotoxic chemotherapy, solid organ or stem cell transplantation, long acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids.

Recommendation 12: The IDSA panel recommends SARS-CoV-2 RNA testing (*versus* no testing) in asymptomatic individuals before immunosuppressive procedures regardless of a known exposure to COVID-19 (strong recommendation, very low certainty of evidence).

Remarks:

- This recommendation defines immunosuppressive procedures as cytotoxic chemotherapy, solid organ or stem cell transplantation, long acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids.
- Testing should ideally be performed as close to the planned treatment/procedure as possible (e.g. within 48-72 hours).
- Many of these patients require frequent, repeated or prolonged visits to receive treatment.
- This recommendation does not address risks or strategies to deal with SARS-CoV-2 transmission in outpatient settings such as infusion centers.

Summary of evidence: We did not identify any studies that directly assessed a strategy of testing for SARS-CoV-2 *versus* no testing of asymptomatic individuals before receiving chemotherapy or transplantation. In addition, we were unable to evaluate the risks of delaying necessary treatments or transplants if testing was not available and quarantine/delay of treatment was then required. We also did not identify any test accuracy studies directly assessing the performance of NAAT in asymptomatic individuals. Based on existing evidence supporting that asymptomatic or pre-symptomatic patients may have similar virus loads and

shedding as those who are symptomatic [62, 63], the panel agreed that test accuracy data from symptomatic patients would apply to asymptomatic populations being hospitalized.

It was essential to determine the pre-test probability or prevalence of COVID-19 in asymptomatic patients who will be receiving chemotherapy. We assessed studies that evaluated prevalence of COVID-19 among asymptomatic individuals and patients with cancer to estimate prevalence a between <1 to 10%. We identified three studies reporting data on the prevalence of cancer among COVID-19 patients and the percentage of complications (e.g., ICU admission, death) among these patients. Liang et al [67] showed that the prevalence of cancer among COVID-19 patients to be 1%, which was higher compared to their general population (0.2%). Yu et al [21] showed the prevalence of COVID-19 among patients admitted to the radiation and medical oncology floor to be 0.8%. Lastly, a systematic review conducted by Desai et al. (2020) [68] showed the pooled prevalence of cancer among COVID-19 cases to be 2-3%. The overall certainty of the evidence about testing effects in immunocompromised individuals was very low due to extremely limited data in this population.

The panel determined that a maximum threshold of <2-5 missed cases per 1000 would be acceptable. Not testing individuals regardless of low *versus* high prevalence areas would lead to higher numbers of missed cases which the panel considered to exceed the acceptable threshold. The threshold was set very low due to concern about catastrophic outcomes in this population.

Benefits and harms: Although data is limited, there are reports documenting outbreaks of respiratory viruses in hospitalized immunocompromised hosts [69]. In addition, increased risks of severe adverse respiratory virus-related outcomes in this population are documented [70]. A higher percentage of ICU admissions among cancer patients with COVID-19 (39% *versus* 8% among non-cancer patients) has been reported [67]. The panel considered that patients who will receive chemotherapy or a transplant could suffer catastrophic outcomes if they have undiagnosed COVID-19; hence, the strong recommendation in the setting of very low certainty

evidence. The potential of nosocomial transmission of disease in an inpatient ward of high-risk patients could also result in serious disease with poor outcomes.

Additional considerations: While the panel recognized that testing capacity may be limited in some settings, the risk of not testing patients in this population and subsequent potential for nosocomial transmission and/or rapid progression of infection resulting in death would outweigh the benefits of not testing. Testing in the 48 hours before a single procedure or treatment is logistically much simpler than situations that involve repeated cycles of chemotherapy for example. In the latter scenario, there is potential for community exposure in between clinic visits. The optimal timing and need for repeated testing over a treatment course in the outpatient setting is not addressed in this recommendation.

Conclusions and research needs for this recommendation: The limited data available indicates that immunocompromised patients have increased risk of severe outcomes from COVID-19 disease. Therefore, testing asymptomatic patients at the time of hospital admission or before initiation of immunosuppressive therapy or transplantation surgery is warranted (e.g., testing within 48 hours). Patients in the outpatient setting who require frequent clinic or infusion room visits should be screened regularly with a standardized questionnaire for symptoms and known exposures in between visits.

Although case reports of disease in patients with malignancies or transplants recipients are accumulating, more information is needed. Research on viral detection, longitudinal follow-up of viral shedding, and clinical outcomes in immunocompromised patients due to multiple underlying conditions are necessary. Definition of the impact of antiviral therapy in this high-risk population is also needed, particularly as many of these patients may have not meet enrollment criteria for treatment trials.

Recommendation 13: The IDSA panel suggests for SARS-COV-2 RNA testing in asymptomatic individuals (without known exposure to COVID-19) who are undergoing major time-sensitive surgeries (conditional recommendation, very low certainty of evidence).

Remarks:

- The panel defined time-sensitive surgery as medically necessary surgeries that need to be done within three months**.**
- Testing should ideally be performed as close to the planned surgery as possible (e.g. within 48-72 hours).
- To limit potential poor outcomes, deferring non-emergent surgeries should be considered for patients testing positive for SARS-CoV-2.
- Decisions about PPE use for the aerosol generating portions of these procedures may be dependent on test results when there is limited availability of PPE. However, there is a risk for false negative test results, so caution should be exercised by those who will be in close contact with/exposed to the upper respiratory tract (e.g., anesthesia personnel, ENT procedures).
- The decision to test asymptomatic patients will be dependent on the availability of testing resources.
- This recommendation does not address the need for repeat testing if patients are required to undergo multiple surgeries over time.

Recommendation 14: The IDSA panel suggests against SARS-CoV-2 RNA testing in asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when PPE is available (conditional recommendation, very low certainty of evidence).

Remark:

- The panel defined time-sensitive procedures as medically necessary procedures that need to be done within three months**.**
- Procedures considered to be aerosol generating are listed in **Table 9**.

Recommendation 15: The IDSA panel suggests SARS-CoV-2 RNA testing in asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when PPE is limited, and testing is available (conditional recommendation, very low certainty of evidence).

Remark:

- The panel defined time-sensitive procedures as medically necessary procedures that need to be done within three months**.**
- Testing should be performed as close to the planned procedure as possible (e.g. within 48-72 hours).
- Decisions about PPE will be dependent on test results because of limited availability of PPE. However, there is a risk for false negative test results, so caution should be exercised for those who will be in close contact with/exposed to the patient's airways.
- Procedures considered to be aerosol generating are listed in **Table 9**.
- The decision to test asymptomatic patients will be dependent on the availability of testing resources.
- This recommendation does not address the need for repeat testing if patients are required to undergo multiple procedures over time.

Summary of evidence: The panel did not identify any studies that directly assessed a strategy of testing for SARS-CoV-2 *versus* no testing of asymptomatic individuals before undergoing major surgery or aerosol generating procedures (AGPs). The panel also did not identify test accuracy studies directly assessing the performance of SARS-CoV-2 NAATs in asymptomatic individuals. However, based on existing evidence supporting that asymptomatic or pre-symptomatic patients may have similar viral loads and shedding as those who are symptomatic, the panel agreed that test accuracy data from symptomatic patients could be applied to asymptomatic populations before surgery.

It was essential to determine the pre-test probability or prevalence of disease in the asymptomatic patients who will undergo surgery. We assessed studies that evaluated the

prevalence of COVID-19 among asymptomatic individuals and determined that the range of prevalence would be between <1 to 10% based on assessing rates of infection in asymptomatic individuals in the general population in low prevalence and in "hotspot" areas [8, 20, 21]. The panel recommendation was based on emphasizing the importance of preventing infection in healthcare providers during major time-sensitive surgeries and AGPs. In addition, the limited data showing poor outcomes in COVID-19 positive patients undergoing a major surgical procedure requiring intubation informed decisions to reduce this risk for asymptomatic patients [71]. There are no data that assess the outcome of AGPs in SARS-CoV-2 positive patients.

Benefits and harms: The benefit of suggesting testing for SARS-CoV-2 in asymptomatic patients undergoing major time-sensitive surgery is that it allows for the identification of infected patients before the procedure; thus allowing surgery to delayed based on the limited data suggesting that patients testing positive may have poor outcomes [71]. This approach also has the potential to inform healthcare workers in terms of PPE use, particularly in areas where PPE is limited. Of note, there is very low certainty evidence from retrospective case series suggesting poor outcomes of time-sensitive surgeries for those with COVID-19. The surgeries included were variable in complexity and it was not clear if the poor outcomes came mostly from major or minor surgeries. However, it is plausible that poor outcomes were driven by the major surgeries.

A potential harm of testing of immunocompetent, asymptomatic patients before a major surgery or AGP is depletion of testing supplies and the diversion of all associated resources away from symptomatic patients. An additional harm of testing is related to the sensitivity of the NAATs for SARS-CoV-2, which will not detect all asymptomatic patients with COVID-19 infection. Therefore, some patients may be missed and healthcare workers at high risk could be exposed. Thus, the panel suggests that healthcare workers at the highest risk during surgical procedures (e.g., those performing intubation or ENT procedures) consider wearing PPE at all times, regardless of test results. This would be especially important in high prevalence areas

(i.e., "hotspots"). An additional harm is that false positive tests for SARS-CoV-2 may unnecessarily delay a major time-sensitive surgery.

Additional considerations: There is no standard definition of what constitutes a major surgery. In general, the panel in consultation with surgical colleagues, agreed that major surgeries would be defined as more complicated and/or prolonged surgeries that require general anesthesia and intubation (which is an AGP). Additionally, time-sensitive surgeries/procedures were defined as those for which a delay greater than 3 months would negatively affect outcomes.

The panel prioritized two factors concerning these recommendations, namely avoidance of spread of COVID-19 to healthcare workers during AGPs as well as minimizing the risk of poor outcomes in patients undergoing major time-sensitive surgery when infected with SARS-CoV-2. There is no evidence of poor outcomes for patients with COVID-19 after AGPs. In these cases, testing could be considered to aid in decisions when PPE is limited. It should also be noted that the CDC does not prioritize asymptomatic patients undergoing procedures or surgeries for testing [72]. However, the panel felt that it is reasonable to consider these patients in local or state plans based on the availability of testing. Ideally, if PPE availability were unlimited, all healthcare workers should wear PPE for all AGPs and major time-sensitive surgeries. The strategy of no testing eliminates the risk of false negative test results missing asymptomatic patients with COVID-19 infection but would increase use of PPE. In contrast, without testing, it would not be possible to identify asymptomatic patients with SARS-CoV-2 undergoing major time-sensitive surgery who might be at risk of poor outcomes. The feasibility of performing NAAT for SARS-CoV-2 for all asymptomatic patients undergoing AGPs and major time-sensitive surgeries will be impacted by the availability of testing as well as the turnaround time of the test results to providers. Logistically, individual institutions will need to decide whether a strategy of test and triage PPE or just use PPE matches available resources. An additional complexity is the need for repeated procedures or surgeries over time. Whether, and when, to retest should be considered on a case by case basis based on the potential risk for exposure in between procedures/surgeries.

Conclusions and research needs for this recommendation: Emergency surgeries and procedures should not be delayed for testing. Decisions around SARS-CoV-2 RNA testing before non-emergency, time-sensitive major surgeries and AGPs hinges on whether results will be used to inform optimal timing of the surgery and/or PPE requirements. The timing of testing should generally be within the 48 hours before the procedure. There are several important areas for future research, including assessing COVID-19 attributable outcomes after surgical procedures performed in the setting of an active infection and determining the risk of AGPs in asymptomatic individuals.

Table 9. Various Organizations' list of Aerosol-Generating Procedures*

Organization	CDC (COVID-19 guidance)[1]	CDC (Seasonal influenza guidance)[2]	WHO (COVID-19 guidance)[3]	WHO (Epidemic and pandemic - prone acute respiratory diseases)[4]
Procedures listed	Open suctioning of airways, sputum induction, cardiopulmonary resuscitation, endotracheal intubation and extubation, non-invasive ventilation (e.g., BiPAP, CPAP), bronchoscopy, manual ventilation	Bronchoscopy, sputum induction, elective intubation and extubation, autopsies, cardiopulmonary resuscitation, emergent intubation and open suctioning of airways	Tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, and bronchoscopy	Aspiration of respiratory tract, intubation, resuscitation, bronchoscopy, autopsy

*Accessed April 16, 2020

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Narrative Summaries of Diagnostics Undergoing Evaluation

In addition to the clinical questions addressed above, there is significant interest in the use of serologic SARS-CoV-2 tests both for diagnosis and public health surveillance. At the time of our literature review, however, additional data were needed to formulate recommendations. Important areas that need to be addressed include assessment of the sensitivity and specificity of commercial antibody tests, determinations of protective immunity and measures of antibody responses over time. Whether seroconversion can inform return to work or hospital staffing policies needs to be assessed. In the absence of evidence to guide the use of SARS-CoV-2 serologic testing, the IDSA Diagnostics Committee published a serology primer for clinicians which highlights potential benefits, limitations and unmet research needs [73].

Antigen detection tests may be on the horizon. How these will compare with NAAT needs to be defined. In addition, current NAATs detect viral RNA but cannot distinguish infectious from non-infectious virus. This determination requires viral culture, which is not routinely performed in clinical laboratories for biosafety reasons and is likely less sensitive than NAAT. It will be important to define whether individuals who remain nucleic acid positive after symptom resolution, and potentially seroconversion, are infectious to others because this will have important ramifications for quarantine and reducing restrictions around social distancing. Some "test of cure" algorithms require two sequential negative NAATs, yet some studies describe prolonged RNA positivity. Future studies are required to determine the significance of nucleic acid or antigen shedding after clinical recovery.

Discussion

Molecular tests designed to detect SARS-CoV-2 nucleic acids are essential both for confirming COVID-19 diagnosis and for public health responses aimed at curbing the pandemic. Several countries have deployed NAAT on a massive scale as the cornerstone of a successful containment strategy. Although the U.S. was hampered by limited test availability early in the outbreak, there are now more than 25 different commercially available SARS-CoV-2 assays and multiple clinical laboratories have developed their own laboratory-developed tests. Aggressive efforts are underway to assure access to testing, but regional differences in availability persist. Individual medical centers and clinics are likely to have different testing capacity as well. Furthermore, which test a laboratory or facility chooses to perform will vary based on the resources of a given setting (e.g., near-patient *versus* high complexity laboratory) and turn-around-time to result requirements (i.e., rapid *versus* standard).

The primary recommendations set forth in this guideline assume that SARS-CoV-2 testing is available to healthcare providers on the front lines. However, the panel also recognized that resources may vary, and contingency recommendations were developed for situations where NAAT supplies or PPE are limited. Individual institutions will need to prioritize testing based on available resources and unique patient populations. Testing for symptomatic patients should be prioritized. When testing capacity for symptomatic individuals is considered sufficiently robust, testing for asymptomatic individuals should be considered. There will undoubtedly be challenges prioritizing and implementing testing strategies for asymptomatic groups. The strongest recommendation for testing in asymptomatic individuals in this guideline pertains to immunocompromised patients being admitted to the hospital or in advance of immunosuppressive procedures.

Molecular tests have been central to our understanding of SARS-CoV-2. However, much about the biology of SARS-CoV-2 remains unknown. Early experience suggests that SARS-CoV-2 is detectable in the upper respiratory tract, with peak levels typically measurable during the first week of symptoms [48, 62, 74]. RNA detection rates, however, appear to vary from patient to patient and change over time. Some patients with pneumonia, for example, have negative upper respiratory tract samples but positive lower airway samples [35, 75]. Much less it known about the frequency of viral detection in asymptomatic individuals, although the concentration of detectable virus in some people with infection may be quite high [62, 63]. A better understanding of the spectrum of viral load kinetics over time at different anatomic sites is needed to inform decisions about the optimal testing strategies, including when and how to repeat if the first test is negative. Like other respiratory viruses, shedding of viral RNA in respiratory secretions may persist beyond resolution of symptoms and seroconversion [76]. Whether such patients remain infectious to others is uncertain and this is an important area for future study.

The clinical performance of commercially available SARS-CoV-2 molecular diagnostic tests has not yet been defined and will depend in large part on the biology of the virus. Typically, when tests for the detection of viral respiratory pathogens are submitted to the FDA, both analytical and clinical performance data are provided. Under EUA, however, only analytical data are required. Diagnostic developers may test contrived specimens, by spiking viral RNA or inactivated virus into the desired matrix, rather than using real clinical specimens collected from patients with COVID-19. Thirty contrived positive and 30 negative specimens tested, with 95% sensitivity and 100% specificity required for EUA. Therefore, while we have information regarding the limit of detection of the test and evidence (both *in vitro* and *in silico* studies) that the primer design is specific for SARS-CoV-2, there is no information on how each test performs clinically at the time the EUA is issued. Clinical laboratories using commercial EUA tests must verify analytic test performance at some level in their own hands, including evaluation of different specimen types and collection methods (e.g., swab types and transport media).

Clinical performance metrics include sensitivity, which is the ability of the test to correctly identify those with infection, and specificity, the ability of the test to correctly identify those without the disease. In practice, the positive and negative predictive values of the test are also essential for interpreting test results. Estimations of community prevalence and patient pre-test probability combined with knowledge of test sensitivity and specificity are essential for determining the likelihood that an individual has COVID-19. In practice, however, the true prevalence of COVID-19 in the community may not be well-defined and may be underestimated when test availability is limited. In addition, while SARS-CoV-2 RNA tests are highly specific, their respective sensitivities are likely to vary. Recognizing these complexities, estimates of prevalence/pre-test probability and assay sensitivity were varied in our analyses based on the available literature in an attempt to mirror what may be encountered in clinical practice. Going forward, robust prevalence studies are needed. Clinical test performance should also ideally be determined in prospective multicenter studies using a well-defined reference standard as the benchmark for test comparisons. **Table 2** outlines the type of clinical studies needed to address the most pressing COVID-19 diagnostic knowledge gaps.

One of the most important problems with current COVID-19 diagnostic literature is the lack of a standard definition to define COVID-19. The studies included in the systematic reviews that informed this guideline used variable case definitions and many classified disease based in part on the results of the index test under investigation. Incorporation of the investigational index test into the diagnostic "gold" standard falsely inflates sensitivity and specificity estimates (i.e. incorporation bias). **Table 10** outlines options for defining a confirmed COVID-19 case in diagnostic trials. It is recognized that not all individuals with COVID-19 will have detectable SARS-CoV-2 nucleic acid. Therefore, a "probable" case definition is also proposed. False negative NAAT results may be due to a variety of factors, including assay limit of detection, anatomic location and adequacy of specimen collection, timing of sampling relative to symptom onset, and underlying biology of disease. To fully understand SARS-CoV-2 viral dynamics, studies need to be designed to obtain specimens from multiple sites, ideally from the same patient at the same time. In addition, information on the duration of symptoms (if present),

assessment of potential exposures and longitudinal follow-up of outcomes will be essential to define optimal diagnostic test strategies across a variety of patient populations.

Table 10. Proposed options for a diagnostic reference standard

CONFIRMED CASE OF COVID-19	
OPTION 1	Nucleic acid sequencing matches SARS-CoV-2 reference sequences
OPTION 2	Positive results from at least 2 different NAATs (one of the two may be the index test)
OPTION 3	Dual positive results from a single NAAT targeting 2 different genes (cannot be the index test)
OPTION 4	Compatible clinical signs and symptoms in a setting with known community transmission, negative reference NAAT and documented SARS-CoV-2 seroconversion.
OPTION 5	Compatible clinical signs and symptoms in a setting with known community transmission, negative reference NAAT and positive index test from two different anatomic sites.
PROBABLE CASE OF COVID-19	
OPTION 1	Compatible clinical signs and symptoms in a setting with known community transmission, negative reference NAAT and positive SARS-CoV-2-specific serology.

Conclusion

The guideline panel used a methodologically rigorous process to critically appraise the available diagnostic literature and formulate SARS-CoV-2 testing recommendations. The quality of existing evidence, however, was limited and not all of the data used to inform these recommendations had undergone peer-review. Based on low certainty evidence, the IDSA panel recommends nucleic acid testing for all symptomatic individuals suspected of having COVID-19. In addition, testing selected asymptomatic individuals is suggested when the results will have significant impact on isolation/quarantine/PPE usage, dictate eligibility for surgery, or inform use of immunosuppressive therapy. Ultimately, institutional resources will dictate test prioritization strategies. The critical components of future COVID-19 diagnostic studies include

use of a well-defined reference standard with detailed descriptions of specimen types, collection methods and their timeframe after symptom onset or exposure to a laboratory-confirmed case.

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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

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