Last updated December 23, 2020 and posted online at www.idsociety.org/COVID19guidelines/dx.

Please check website for most updated version of these guidelines. Supplementary materials can be found here.

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

Authors

Kimberly E. Hanson,[1] Angela M. Caliendo,[2] Cesar A. Arias,[3] Mary K. Hayden,[4] Janet A. Englund,[5] Mark J. Lee,[6] Mark Loeb,[7] Robin Patel,[8] Abdallah El Alayli,[9] Osama Altayar,[10] Payal Patel,[11] Yngve Falck-Ytter,[12] Valery Lavergne,[13] Rebecca L. Morgan,[14] M. Hassan Murad,[15] Shahnaz Sultan,[16] Adarsh Bhimraj,[17] Reem A. Mustafa[18]

Affiliations

[1]Department of Internal Medicine and Pathology, University of Utah, Salt Lake City, Utah

[2]Department of Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island

[3]Division of Infectious Diseases, Center for Antimicrobial Resistance and Microbial Genomics, University of Texas Health McGovern Medical School, Center for Infectious Diseases, University of Texas Health School of Public Health, Houston, TX

[4]Division of Infectious Diseases, Department of Medicine, Rush University Medical Center, Chicago, Illinois; Department of Pathology, Rush University Medical Center, Chicago, Illinois

[5]Department of Pediatrics, University of Washington, Seattle Children's Research Institute, Seattle, Washington

[6]Department of Pathology and Clinical Microbiology Laboratory, Duke University School of Medicine, Durham, North Carolina

[7]Divinsion of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario

[8]Division of Clinical Microbiology, Mayo Clinic, Rochester, Minnesota

[9]Outcomes and Implementation Research Unit, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas

[10]Department of Medicine, Washington University School of Medicine, St. Louis, Missouri.

[11]Department of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, Emory University, Atlanta, Georgia

[12]VA Northeast Ohio Healthcare System, Case Western Reserve University School of Medicine, Cleveland, Ohio

[13]Department of Pathology and Laboratory Medicine, Vancouver General Hospital, Vancouver, British Columbia, Canada

[14]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario

[15]Division of Preventive Medicine, Mayo Clinic, Rochester, Minnesota

[16]Division of Gastroenterology, Hepatology, and Nutrition, University of Minnesota, Minneapolis VA Healthcare System, Minneapolis, Minnesota

[17]Department of Infectious Diseases, Cleveland Clinic, Cleveland, Ohio

[18]Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas

Corresponding Author: Kimberly E. Hanson

Panel Members: Kimberly E. Hanson (lead), Angela M. Caliendo, Cesar A. Arias, Mary K. Hayden, Janet A. Englund (PIDS representative), Mark J. Lee, Mark Loeb (SHEA representative), Robin Patel (ASM representative), Adarsh Bhimraj

Methodologists: Reem A. Mustafa (lead), Abdallah El Alayli, Osama Altayar, Payal Patel, Yngve Falck-Ytter, Valery Lavergne, Rebecca L. Morgan, M. Hassan Murad, Shahnaz Sultan

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 assist 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 17 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 moderate 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 solid organ or hematopoietic stem cell transplantation timing. 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.

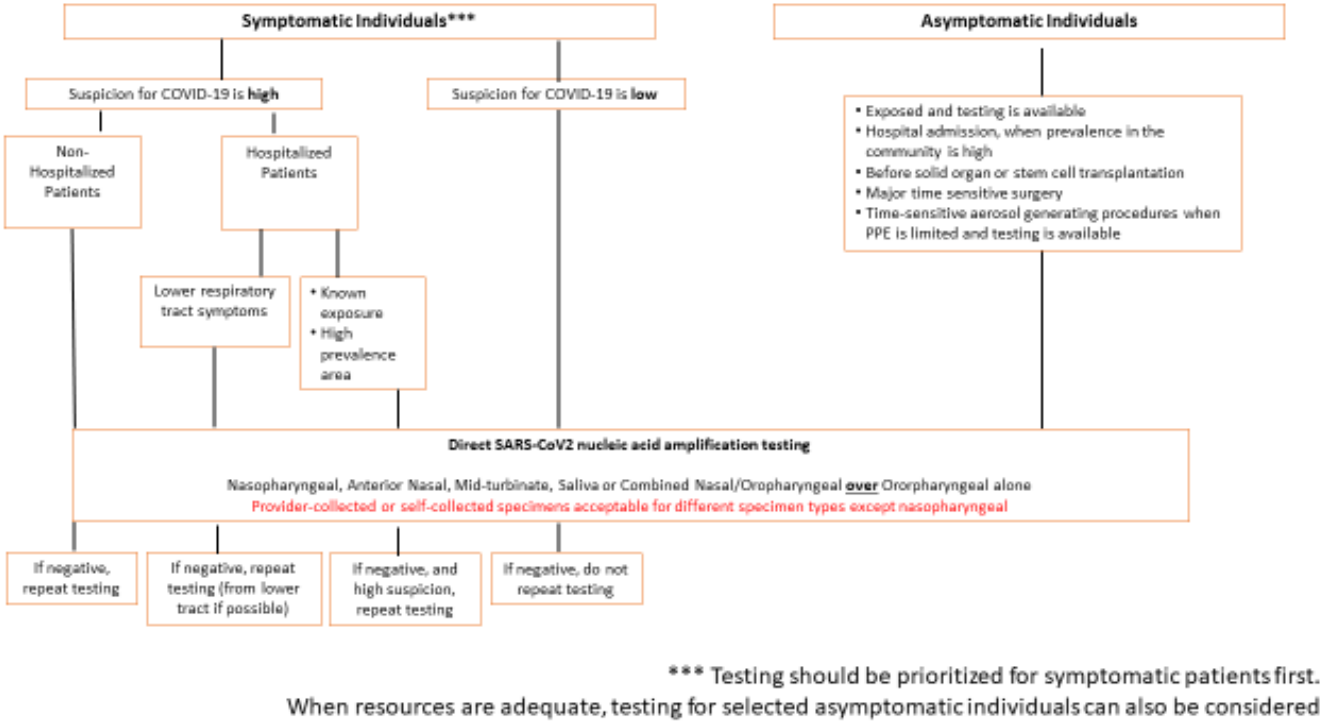
Executive Summary

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 17 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



Recommendation 1: The IDSA panel recommends a SARS-CoV-2 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 a nasopharyngeal swab, mid-turbinate swab, anterior nasal swab, saliva or a combined anterior nasal/oropharyngeal swab rather than

an oropharyngeal swab alone for SARS-CoV-2 RNA testing in symptomatic individuals suspected of having COVID-19 *(conditional recommendation, very low certainty of evidence)*.

- **Remark**: 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 anterior 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 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-CoV-2 testing are shown in **Table 3**. 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 suggests using either rapid RT-PCR or standard laboratory-based NAATs over rapid isothermal NAATs in symptomatic individuals suspected of having COVID-19 *(conditional recommendation, low certainty of evidence).*

- **Remarks**:
  - Rapid NAAT was defined as assays generating results in approximately one hour or less of instrument run time (inclusive of nucleic acid extraction).
  - This recommendation only applies to the tests evaluated in the included studies (**Table s4f**).
  - Standard laboratory-based NAAT methods evaluated included RT-PCR and transcription mediated amplification (TMA).
  - Studies of rapid isothermal NAAT primarily used the Abbott ID NOW test
  - Rapid isothermal NAAT is an acceptable testing option when rapid RT-PCR or standard laboratory-based NAAT is not readily available.
  - A negative rapid isothermal test result from an individual with a high clinical suspicion for SARS-CoV-2 infection, or anyone in a moderate (10%) or high prevalence (40%) population, should be confirmed by standard NAAT or a rapid RT-PCR test when testing is available and the results will affect patient management.

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 suggests 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 ³10%.
- 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)*.

- **Remark**: This recommendation defines immunosuppressive procedures as cytotoxic chemotherapy, solid organ or stem cell transplantation, 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 hematopoietic stem cell (HSCT) or solid organ transplantation (SOT) regardless of a known exposure to COVID-19 *(strong recommendation, very low certainty of evidence)*.

- **Remark:** Testing should ideally be performed as close to the planned treatment/procedure as possible (e.g., within 48-72 hours).

Recommendation 13: The IDSA panel makes no recommendations for or against SARS-CoV-2 RNA testing before initiating immunosuppressive therapy in asymptomatic individuals with cancer *(evidence gap)*.

- **Remarks**:
  - The decision to pursue testing should be individualized. Factors to consider include the type of cancer, the need for induction *versus* maintenance immunosuppressive

therapy, the type of immunosuppressive therapy, patient comorbidities and the availability of testing.

- This recommendation does not apply to hematopoietic stem cell transplant candidates or recipients.

Recommendation 14: The IDSA panel makes no recommendations for or against SARS-CoV-2 RNA testing before the initiation of immunosuppressive therapy in asymptomatic individuals with autoimmune disease *(evidence gap)*.

- **Remark**: The decision to pursue testing should be individualized. Factors that may affect the decision to test include the type and severity of autoimmune disease, the type of immunosuppressive therapy, the need for induction *versus* maintenance immunosuppressive therapy, patient comorbidities and the feasibility of testing.

Recommendation 15: The IDSA panel suggests 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 16: 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 11**.

Recommendation 17: 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)*.

- **Remarks**:
  - 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 11**.

- 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 designed to detect one or more gene sequences specific to SARS-CoV-2 are essential for confirming COVID-19 diagnoses. On February 4, 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**.

It is anticipated that these guidelines will continue to be updated as substantive new information becomes available.

Table 1. Symptoms Compatible with COVID-19 [1,2]

Symptoms may appear **2-14 days after exposure to the virus.** People with these symptoms or combinations of symptoms may have COVID-19*	Most common symptoms* • Cough • Shortness of breath or difficulty breathing • Fever Additional reported symptoms • Chills • Fatigue • Muscle pain • Headache • Sore throat • New loss of taste or smell • Congestion or runny nose • Nausea or vomiting • Diarrhea

*This list is not all inclusive. Fever, cough or shortness of breath were the most common symptoms reported among a convenience sample of U.S. COVID-19 patients

References

1. 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.
2. Burke RM, Killerby ME, Newton S, et al. Symptom Profiles of a Convenience Sample of Patients with COVID-19 — United States, January–April 2020. Morbidity and Mortality Weekly Report - CDC **2020**; 69(28): 904-8.

Methods

The 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 Guidelines International Network/McMaster checklist for development of rapid recommendations [6]. This guideline serves as an update to the original IDSA Guidelines on the Diagnosis of COVID-19 [7], and focuses on the performance of different specimen types for the detection of SARS-CoV-2 RNA (recommendation 2), the accuracy of rapid versus standard laboratory-based nucleic acid amplification tests (recommendation 7) as well as molecular diagnostic testing before immunosuppressive therapy in selected groups of patients (recommendations 12, 13 and 14).

Panel Composition

The panel was composed of eight members including frontline clinicians, infectious diseases specialists, and clinical microbiologists who were members of 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

For the original guideline, clinical questions were developed into a Population, Intervention, Comparison, Outcomes (PICO) format [8] 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. In this update, the panel focused on the questions addressing rapid tests and different sample types for the diagnosis of COVID-19 as well as testing before immunosuppressive therapy for the treatment of cancer or autoimmune disease.

Search Strategy

The National Institute of Health and Care Excellence (NICE) and the Center for Disease Control and Prevention (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 databases were searched for studies from 2019 through October 3, 2020. Horizon scans were performed during the evidence assessment and recommendation process to locate additional grey literature, manuscript preprints, and published literature from 2019 to August 20, 2020 from the following sources: LitCovid, medRxiv, SSRN, and Trip databases. The preprints were followed for final publication. In this update, the panel decided not to include studies that are solely published in preprint format due to the sufficient number of published studies identified. 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 all tests in the same population, referred to as direct comparative test accuracy studies. For this analysis, studies were excluded if all patients did not receive all tests. 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.

Exclusion criteria for studies that assessed rapid testing were studies evaluating an index test that was not a rapid molecular test (sample to result was >1 hour turnaround time), studies focused on a specific population rather than general diagnostic data (i.e., focused on test accuracy in patients with specific cycle thresholds), studies with incomplete test accuracy information (i.e., reported sensitivity without specificity), and studies where the endpoint of

the rapid test was based on visual inspection of result. Patients that were known COVID-19 positive but were tested in the recovery phase of illness and patients with invalid or inconclusive results were also excluded from the analysis. In addition, patients were presumed positive if an assay provided a positive result for at least one gene. For example, if two genes are tested on a single assay, a minimum of one gene needed to be positive to presume the patient as a positive result for that test.

For the direct comparative test accuracy studies (including rapid versus standard tests), data was abstracted with each test as the index test and the combination of tests as a reference standard. The panel determined the combination of tests reference standard would be a minimum of at least two positive tests. For example, if one out of four tests were positive, this patient would be considered negative. If two out of four tests were positive, this patient would be considered positive. In addition, when the same population received more than one standard test, the panel determined which test to use for the direct comparative analysis, as pooling all of the standard tests from a single study would duplicate the same population.

Exclusion criteria for studies that assessed test accuracy based on sample type were studies with fewer than 10 patients, studies with incomplete test accuracy information (i.e., reported sensitivity without specificity), studies that did not report synchronous collection of different sample, studies that reported test accuracy results in recovering patients or with samples collected ≥7 days since symptom onset, and studies that reported results as a number of samples and not as a number of patients.

For patients with autoimmune conditions or cancer, studies assessing the outcomes of COVID-19 if a pre-testing strategy before the initiation of immunosuppressive therapy was utilized could not be identified. Thus, studies that indirectly informed the PICO questions were included. Those included studies of the outcome of COVID-19 in patients with autoimmune conditions or cancer, and the outcomes of COVID-19 in patients receiving treatments for autoimmune conditions or cancer. The role of testing in transplant patients was not prioritized in this update.

Data Collection and Analysis

Two reviewers completed data extraction independently and in duplicate. Reviewers extracted relevant information into a standardized data extraction form. 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 pooled quantitatively using the logit transformation and the bivariate random effects model, when there were enough studies, which accounts for between study variation as well as the correlation between sensitivity and specificity. We used the random effects generalized linear mixed models to pool the sensitivity and specificity separately when it was not possible to conduct the bivariate model, and as a sensitivity analysis when the bivariate model was conducted. The Freeman-Tukey double arcsine transformation was used when there were no false negatives or false positives [9, 10]. The between study heterogeneity was assessed by examining the forest plots. When the analysis included studies that used different sample types and/or transport media for the index and reference tests, we conducted sensitivity analyses that excluded those studies to assess the robustness of our findings. The analyses were performed using the packages mada 0.5.10 and meta 4.11.0 in R 3.6.3 [11-13].

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. Prevalence, as defined by the results of surveillance testing in a given community, has been shown to change overtime. For the purposes of the guideline, we used a prevalence of <2% to represent asymptomatic individuals in a community with ongoing SARS-CoV-2 transmission, 10% to represent symptomatic outpatients (although this may be much higher in some locations), 40% for

patients with compatible signs and symptoms being admitted to the hospital and as high as 80% for those admitted to the ICU.

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**) [14]. 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 [15, 16]. GRADE summary of findings tables were developed in GRADEpro Guideline Development Tool [17].

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) [18]. For recommendations pertaining to good practice statements, appropriate identification and wording choices were followed according to the GRADE working group [19]. 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.

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.

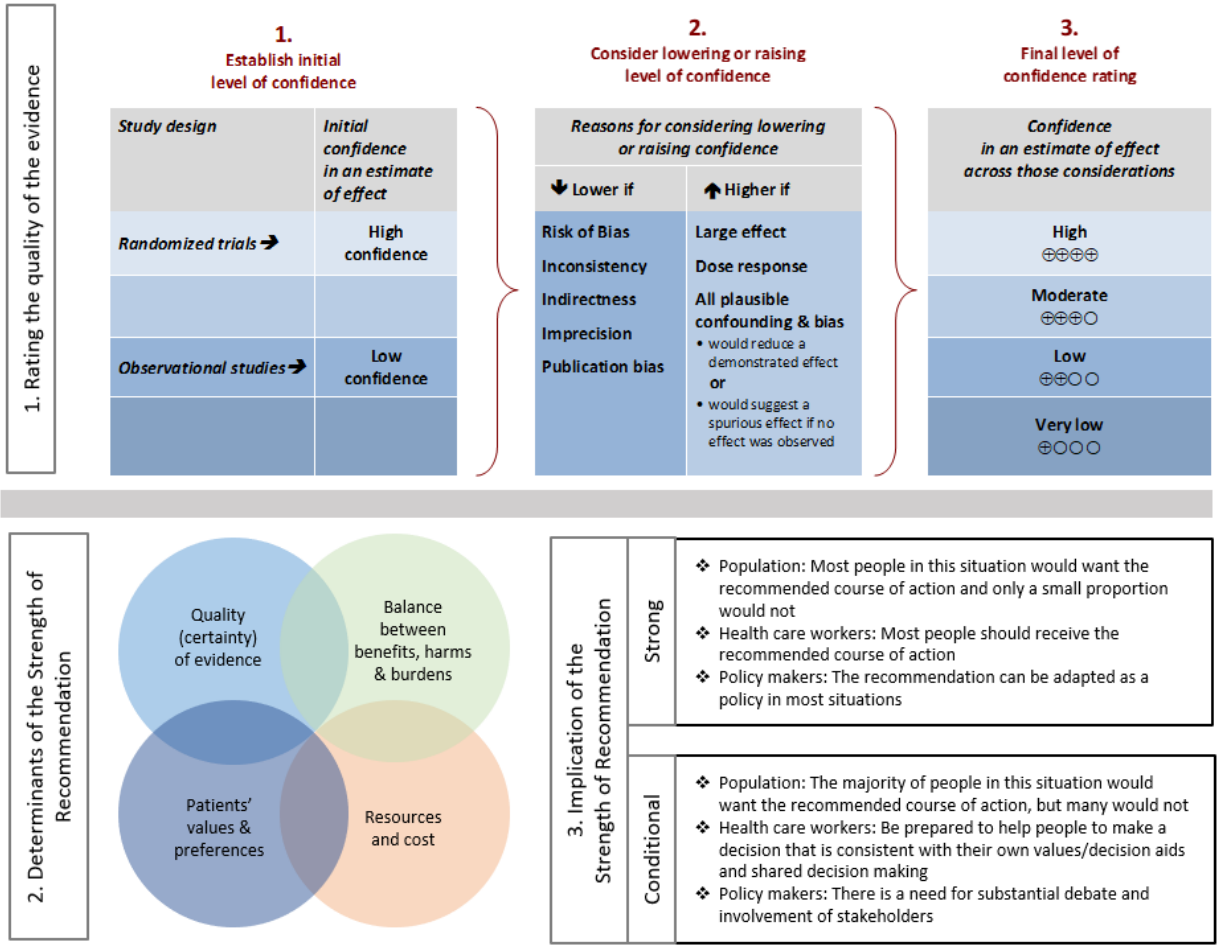
Updating Process

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.

Search Results

Systematic review and horizon scan of the literature identified 26,536 references, of which 560 full texts and 12 systematic reviews were reviewed. Nineteen studies informed the evidence base for the rapid testing recommendations, 26 studies informed the evidence base for the sample type recommendations and 66 manuscripts focused on patients with cancer (excluding transplant recipients) or autoimmune disease were also reviewed (**Figure s1**). Characteristics of the included studies can be found in **Tables s4a-s4m**.

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)



Recommendations

NAAT in Symptomatic Individuals

Recommendation 1: The IDSA panel recommends a SARS-CoV-2 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 [17, 20-26] (**Supplement B**). 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 [17, 21, 24, 26]. Due to the mentioned concerns with the studies and the inconsistency among them, the panel assessed the overall certainty of evidence as very low. However, over the last few months there is an overwhelming indirect evidence documenting

the benefits of testing. Additionally, we have indirect evidence documenting higher certainty about the harms of no testing in populations with widespread community transmission. This recommendation falls under one of the paradigmatic situations for a strong recommendation despite certainty evidence.

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.

Additional considerations

SARS-CoV-2 testing is acceptable to patients and providers. However, testing may not be readily 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 [27, 28]. 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.

Nasopharyngeal, Mid-Turbinate, Anterior Nasal, Saliva, and Oropharyngeal Swabs

Recommendation 2: The IDSA panel suggests collecting a nasopharyngeal swab, mid-turbinate swab, anterior nasal swab, saliva or a combined anterior nasal/oropharyngeal swab rather than an oropharyngeal swab alone for SARS-CoV-2 RNA testing in symptomatic individuals suspected of having COVID-19 *(conditional recommendation, very low certainty of evidence)*.

- **Remark**: 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

We reviewed the published literature to identify studies assessing the performance of different specimen types relative to nasopharyngeal (NP) swabs for the detection of SARS-CoV-2 RNA. Specimen types were grouped into NP swabs, mid-turbinate (MT) swabs (also referred to as "deep nasal" swabs in some studies), anterior nasal (AN) swabs, oropharyngeal (OP) swabs (also referred to as "throat" swabs in some studies), saliva or a combined swab sampling of AN and OP. A swab insertion cutoff of 0.5 inch was used to differentiate between AN and MT

swabs. Due to variability in collection methods, saliva specimens were further subdivided into saliva with coughing, if the study reported asking individuals to cough or clear their throat prior to saliva specimen collection, and saliva without coughing if the study did not report asking individuals to cough prior to the saliva specimen collection. Analyses of "tongue" or "mouth" swabs were excluded due to inadequate study numbers.

Twenty studies [29-48] reported the test accuracy of different sample types using a NP swab as a reference test. Random effects generalized linear mixed model was used to pool the sensitivity and specificity, separately, of alternative sample types *versus* NP swabs as the reference standard. Findings are displayed in **Supplement C**. For the sample types that had enough studies, the random effects bivariate model was conducted and showed comparable pooled estimates. An additional eight studies [49-56] did not use NP swabs as a reference standard and were assessed separately. Summary statistics of the different specimen type are shown in **Table 2**. The overall quality of the evidence was deemed to be low due to a risk of bias introduced by using NP swabs as the reference standard and to be very low when imprecision and/or inconsistency were also present.

Benefits and harms

There are multiple potential benefits of using specimen types other than a NP swab for the molecular diagnosis of SARS CoV-2 infection. Collection of nasal swabs (either AN or MT) and saliva is less invasive than NP sampling and may be more comfortable for patients. In addition, these sample types are amendable to patient self-collection, either at home or in a healthcare setting. This provides flexibility and reduces strain on trained healthcare staff. Compared to NP swab collection, nasal swabs or saliva (collected without coughing) also have less potential to generate infectious aerosols, thus reducing transmission risk to healthcare workers involved in specimen collection. Saliva has the added benefit of being a "swab-free" sample type. Swab supply shortages have been problematic in many locations. In addition, saliva collection vials can be made directly compatible with laboratory robotics, allowing facile processing.

The potential harms of alternative specimen types include false negative and false positive results relative to NP sampling. False negative results may lead to additional transmission events, because infected individuals incorrectly believe there are not infectious to others and therefore do not self-isolate. Or they may lead to patients not receiving appropriate care. False positive results can cause anxiety, have the potential for lost work or school productivity, may lead to the unnecessary use of contact tracing resources and may lead to a missed diagnosis of the true cause of symptoms and possibly administration of unnecessary treatment for COVID-19. NP swabs, however, are an imperfect standard due to potential variability in collection techniques leading to sampling error. Apparent "false positive" saliva or non-NP swab results may actually be true positives, given that these specimens were mostly obtained from symptomatic patients in settings with a moderate prevalence of COVID-19.

Saliva testing requires clinical laboratories to validate this specimen type on their test platforms. Saliva is a complex sample matrix, especially if sputum or mucus is mixed with the sample. Including coughing may theoretically improve specimen quality by sampling the posterior nasopharynx and/or the lower respiratory tract. However, coughing may create exposure risks to those in the vicinity of specimen collection. Coughing may also add more mucus to saliva that can interfere with test performance and negatively affect test results. As a result, saliva testing typically produces a higher number of invalid results compared to swabs in transport media [7] . Such results may cause provider and patient frustration and can be associated with increased cost if repeat testing or sample recollection using an alternative method is required. The need for repeat testing delays reporting of true positive or negative results, which in turn delays isolation decisions, clinical management, and contact tracing around true positive cases.

Additional considerations

COVID-19 testing is performed on both symptomatic and asymptomatic individuals. The majority of studies addressed herein assessed symptomatic subjects. Whether or not these findings are generalizable to asymptomatic individuals is unknown. We note, however, that NP swab viral loads have been shown to be similar in symptomatic and asymptomatic individuals

[25] Additionally, a majority of included studies focused on adult subjects; generalizability of results to children is unknown.

Although the actual types of swabs used were not considered separately in this analysis, there could be performance differences among swab-types (e.g., flocked *versus* non-flocked swabs or natural *versus* synthetic swab tip material) not accounted for in this analysis. Likewise, the process of swab collection may be variable and that inconsistency could have affected results. Some studies sampled unilateral and others bilateral nasal passages. Sampling the nares and throat together may be done with two swabs placed in the same tube or a single swab. The nature and volume of media the swabs were placed into (e.g., type and amount of specific transport media) also varied. Furthermore, different nucleic acid amplification assays, gene targets and interpretive criteria were applied across studies. We only assessed assay results as positive or negative (as defined in the studies analyzed) and did not include signal strength of nucleic acid amplification (e.g., Ct value for real-time PCR assays), which could differ between the sample-types analyzed.

Saliva has not been a common specimen type used for infectious diseases diagnostics and limited data on saliva performance was available for the first version of the IDSA diagnostic guidelines. There is now enough published literature to be able to address saliva testing, but heterogeneity in specimen collection processes used may have affected downstream test performance. In general, saliva collection requires that the patient is able to follow and cooperate with the collection instructions, which may be difficult for individuals with severe symptoms, young children or those with cognitive impairment. As noted, some studies collected saliva with coughing (also referred to as "deep throat saliva" in some studies) and some without coughing using dribbling, drooling or spitting. Some groups have described the use of specimen containers including a short straw, with subjects asked to collect saliva in their mouth and run it down the straw into the tube. The use of a straw avoids aerosolization from spitting and may reduce potential for contaminating the outside of the container but requires active cooperation with the subject. Contamination of the outside of the container is a concern and is possibly mitigated by wiping the container with a virucidal agent or placing the collection

container in another larger one. There were also differences across studies related to use of dilution steps prior to saliva testing or use of collection kits with stabilizing agents, which may impact sensitivity. Lastly, many saliva studies asked subjects to refrain from eating, drinking, chewing gum or tobacco, or smoking for 30 minutes prior to collection, which may not always be feasible in walk-up or "on demand" testing locations.

Conclusions and research needs for this recommendation

Specimen types, including AN swabs, MT swabs, saliva, and a combination of AN/OP, sampling have comparable performance to NP swabs for the detection of SARS-CoV-2 RNA. Saliva with coughing, MT swabs or combined AN/OP samples were the most similar to NP swabs. In contrast, OP swabs alone were the least sensitive sampling modality. Given that NP swabs are an imperfect standard, future studies might consider using a composite gold standard consisting of multiple site sampling to try to improve the reference standard. Studies in pediatric patients (particularly addressing non-invasive specimen-types such as saliva and anterior nares swabs) are needed as are studies in asymptomatic individuals of all ages. Lastly, additional studies of novel oral fluid sampling approaches are needed. Some examples of methods currently under evaluation include collection devices that "wick up" saliva and use colorimetric indicators to tell the subject when enough specimen has been obtained, as well as various 'swish, gargle, and spit' approaches.

Table 2. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 10% for different Specimen Types

Sample site	Saliva without coughing	Saliva with coughing	OP swab	AN swab	MT swab	Combined AN/OP swab
Sensitivity	0.90 (95% CI: 0.85 to 0.93)	0.99 (95% CI: 0.94 to 1.00)	0.76 (95% CI: 0.58 to 0.88)	0.89 (95% CI: 0.83 to 0.94)	0.95 (95% CI: 0.83 to 0.99)	0.95 (95% CI: 0.69 to 0.99)
Specificity	0.98 (95% CI: 0.93 to 1.00)	0.96 (95% CI: 0.83 to 0.99)	0.98 (95% CI: 0.96 to 0.99)	1.00 (95% CI: 0.99 to 1.00)	1.00 (95% CI: 0.89 to 1.00)	0.99 (95% CI: 0.92 to 1.00)
Outcome	**Effect per 1,000 patients tested**					
	Pre-test probability of 10% [a, f]					
True positives (patients with COVID-19)	90 (85 to 93)	99 (94 to 100)	76 (58 to 88)	89 (83 to 94)	95 (83 to 99)	95 (69 to 99)
False negatives (patients incorrectly classified as not having COVID-19)	10 (7 to 15)	1 (0 to 6)	24 (12 to 42)	11 (6 to 17)	5 (1 to 17)	5 (1 to 31)
Quality of the evidence[b,c,d]	9 studies 387 patients ⊕⊕◯◯ LOW[b]	3 studies 137 patients ⊕⊕◯◯ LOW[b]	4 studies 64 patients ⊕◯◯◯ Very LOW[b,d,e]	2 studies 130 patients ⊕⊕◯◯ LOW[b]	5 studies 855 patients ⊕⊕◯◯ LOW[b]	2 studies 61 patients ⊕◯◯◯ Very LOW[b,d,e]
True negatives (patients without COVID-19)	882 (837 to 900)	864 (747 to 891)	882 (864 to 891)	900 (891 to 900)	900 (801 to 900)	891 (828 to 900)

False positives (patients incorrectly classified as having COVID-19)	18 (0 to 63)	36 (9 to 153)	18 (9 to 36)	0 (0 to 9)	0 (0 to 99)	9 (0 to 72)
Quality of Evidence	9 studies 2662 patients ⊕⊕◯◯ LOW[b,c]	3 studies 316 patients ⊕◯◯◯ Very LOW[b,d]	4 studies 368 patients ⊕⊕◯◯ LOW[b]	2 studies 722 patients ⊕⊕◯◯ LOW[b]	5 studies 682 patients ⊕◯◯◯ Very LOW[b,d]	2 studies 237 patients ⊕⊕◯◯ LOW[b]

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. Typically seen in general population in an at-risk population
b. Using the NP swab as a reference standard increases the risk of bias for all the studies.
c. One study with unexplained inconsistent results noted. However, a sensitivity analysis without this study showed robustness of the overall pooled estimate of specificity.
d. Considering the upper and lower limits of the confidence interval might lead to different clinical decisions.
e. The test of interest was conducted in a small number of patients which might lead to imprecise results.
f. The different sample types were not assessed directly in the same studies.

Swab Collection by Patients or Healthcare Providers (Symptomatic)

Recommendation 3: The IDSA panel suggests that anterior nasal and mid-turbinate 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 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-CoV-2 testing are shown in **Table 3**. 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 [57]. 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 [58]; 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 [59]. 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 4**.

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 3. General Instructions for Swab-based SARS-CoV-2 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 (¾1 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

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.

References

1. Centers for Disease Control and Prevention. Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens for COVID-19. COVID-19 (Coronavirus Disease) 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html. Accessed 22 April 2020.
2. U.S. Food and Drug Administration. FAQs on Testing for SARS-CoV-2. 2020. Available at: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2. Accessed 29 April 2020.

Table 4. 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** **pre-test probability of 10%** [c]		**№ of patients (studies)**	**Test accuracy CoE**
	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			

CoE: Certainty of evidence

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

Upper vs. Lower Respiratory Tract Samples

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 [60, 61]. Seven studies reported on sensitivity, of which three had a case control design [62-64] and one reported results per sample and not per patient [65]. The three cohort studies [59, 66, 67] 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 three cohort studies are shown in **Table 5**. 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 5. 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 (three 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**
	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			

CoE: Certainty of evidence

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.

Single vs. Repeating RNA Test (Symptomatic)

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 [17, 68, 69] (**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 two or three days later for repeat testing. Summary statistics for single versus repeated testing are shown in **Table 6**. 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 6. 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**
	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**			

CoE: Certainty of evidence

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

Rapid vs. Standard Laboratory-based NAAT (Symptomatic)

Recommendation 7: The IDSA panel suggests using either rapid RT-PCR or standard laboratory-based NAATs over rapid isothermal NAAT in symptomatic individuals suspected of having COVID-19 *(conditional recommendation, low certainty of evidence).*

- **Remarks**:
  - Rapid NAAT was defined as assays generating results in approximately one hour or less of instrument run time (inclusive of nucleic acid extraction).
  - This recommendation only applies to the tests evaluated in the included studies (**Table s4f**).
  - Standard laboratory-based NAAT methods evaluated included RT-PCR and transcription mediated amplification (TMA).
  - Studies of rapid isothermal NAAT primarily used the Abbott ID NOW test
  - Rapid isothermal NAAT is an acceptable testing option when rapid RT-PCR or standard laboratory-based NAAT is not readily available.
  - A negative rapid isothermal test result from an individual with a high clinical suspicion for SARS-CoV-2 infection, or anyone in a moderate (10%) or high prevalence (40%) population, should be confirmed by standard NAAT or a rapid RT-PCR test when testing is available and the results will affect patient management.

Summary of the evidence

We systematically identified and reviewed published studies evaluating the diagnostic test accuracy of "rapid" *versus* "standard" SARS-CoV-2 NAAT technologies. Rapid tests were defined as those that generate results in approximately one hour or less of instrument run time, exclusive of the time it takes to collect the specimen and transport it to the testing location, but inclusive of any processing and/or extraction required. Rapid tests typically have

few operator steps and are amendable to testing at the point-of-care by non-laboratory staff. Rapid test methodologies include rapid RT-PCR and rapid isothermal NAAT. Standard tests require instrumentation and/or processing that must be performed in a clinical laboratory by trained laboratory staff. Assay run times generally require more than an hour and use RT-PCR or transcription mediated amplification (TMA). **Table s4f** displays the various assays and methodologies that were included in our review.

In all, we identified 19 studies [70-88] that assessed diagnostic test accuracy of rapid RT-PCR or rapid isothermal NAAT *versus* standard methods in symptomatic patients (**Supplement G**). A subset of studies involved a multi-way comparison between three or more SARS-CoV-2 molecular diagnostic tests (i.e., a single rapid test and multiple standard laboratory-based NAATs). The reference standard in these studies was labeled a "composite reference standard," that defined a "positive case" or a "negative case" of SARS CoV-2 infection using a combination of multiple tests. The definition of a "positive case" was set to require at least two out of the total number of tests performed to be positive. These studies allowed a direct comparison of the performance of a rapid test and a standard NAAT against a "composite reference standard" that combined the results of multiple tests. Twelve studies [73-77, 81-84, 86-88] assessed the test accuracy of rapid RT-PCR compared to standard NAAT or a composite reference standard when available and nine studies [70-72, 78-80, 83, 85, 88] assessed the diagnostic test accuracy of rapid isothermal NAAT compared to standard NAAT or a composite reference standard when available. There were four studies comparing rapid RT-PCR and a standard test to a composite reference standard [70, 75, 82, 83, 88] and four studies comparing a rapid isothermal NAAT and a standard test versus a composite reference standard [80, 83, 88].

Rapid RT-PCR tests had a pooled sensitivity of 97% (95% CI: 94-99) with specificity 96% (95% CI: 94-98; **Figure s7a-s7b** and **Table s13**) compared to a single standard NAAT or composite reference standard when available. In the subgroup of studies that allowed direct comparison of the diagnostic accuracy of rapid RT-PCR and standard laboratory-based NAAT using a composite reference standard, the sensitivity and specificity of rapid RT-PCR were comparable to standard laboratory-based tests (98% [95% CI: 95-100] vs. 98% [95% CI: 95-99]

and 97% [95% CI: 89-99] vs. 97% [95% CI: 92-99], respectively; **Table 7** and **Figures s9a-s9b**). Rapid isothermal NAAT had a sensitivity of 70% (95% CI: 56-81) with specificity 99% (95% CI, 97-99; **Figures s8a-s8b and Table s14**) compared to a single standard NAAT or composite reference standard when available. In the subgroup of studies that allowed direct comparison of rapid isothermal tests and standard laboratory-based NAAT using a composite reference standard, rapid isothermal tests had lower sensitivity than standard laboratory-based tests (81% [95% CI: 75-86] vs. 99% [95% CI: 97-100]) but comparable specificity (99% [95% CI: 96-100] vs 97% [95% CI: 93-99]; **Table 8** and **Figure s10**). We explored inconsistency in a sensitivity analysis including only studies that used the same sampling method and transport conditions for both the rapid isothermal test and standard laboratory-based NAAT. Sampling method did not affect the results (**Figures s8c-s8d**). All NAAT methods showed high specificity (i.e., ≥97%).

All the analyses were conducted using the bivariate model, thus we performed sensitivity analyses using the random-effects generalized linear mixed models and the results were comparable. Overall quality of evidence ranged from low to moderate. Quality was downgraded for risk of bias (concerns about different sample sources and transport media, and/or using a single test as a reference standard), inconsistency (variable levels of heterogeneity across the comparisons), and/or imprecision (due to small sample sizes and/or wide confidence interval that may lead to different conclusions).

Benefits and harms

The benefits and harms of SARS-CoV-2 testing need to balance the value of a rapid result against the test performance characteristics of rapid NAAT, which may not be as sensitive as a standard laboratory-based test. The value of obtaining a test result rapidly (within one hour), while the patient is still present, is that it allows patients to be put into isolation and management decisions to be made quickly. A rapid result also decreases concerns of losing patients to follow up and generally makes follow up easier. However, a less sensitive test increases the number of false negative results, which could delay a diagnosis of COVID-19 infection and lead to spread of the disease and miss a management opportunity for infected individuals.

Using rapid RT-PCR and standard laboratory-based tests will minimize false negative results, due to their high sensitivity. The rapid isothermal tests evaluated here had a reduced sensitivity compared to rapid RT-PCR and standard laboratory-based NAAT tests, leading to an increased number of false negative results. Individuals with COVID-19 will test negative and not be isolated as a result of false negative results, thus increasing the potential for spread of the disease. In addition, false negatives may delay opportunities for treatment. The degree of harm is related to the number of false negative isothermal NAAT results, which will vary depending on the prevalence of disease. All rapid and non-rapid molecular tests had a very high specificity, thus minimizing false positive results. The harm of false positive results includes isolating individuals who do not have COVID-19 infection, causing unnecessary anxiety, delaying additional evaluation looking for the cause of symptoms, potentially administering unnecessary therapeutics for COVID-19, and increasing days out of work and contact tracing.

Additional considerations

The vast majority of the studies included in our analysis were conducted on symptomatic individuals, with limited information provided regarding the timing of specimen collection in relationship to the onset of symptoms. Timing of testing relative to symptom onset may have a significant impact on the sensitivity of the test. In addition, there is very limited data on the performance of rapid tests in asymptomatic individuals and in children. Whether our findings are generalizable to these groups is unknown. However, we do note that asymptomatic patients appear to have viral load levels in their respiratory secretions similar to symptomatic individuals [25]

An additional factor that complicated the assessment of the performance of the rapid tests was differences in specimen type and the use of viral transport media (VTM). Some rapid isothermal NAAT studies tested a NP swab sample in VTM, which dilutes the specimen and may reduce the sensitivity of some rapid isothermal tests. In other studies, a dry anterior nasal swab was collected for the rapid isothermal test, while a NP swab in VTM was used as the standard laboratory-based comparator test. These differences in specimen type and dilution of specimens may impact the sensitivity of the rapid isothermal tests. Lastly, there were no

studies directly comparing rapid isothermal NAAT and rapid RT-PCR tests to one another, which precludes the direct comparisons of different rapid test performance.

Conclusions and research needs for this this recommendation

The sensitivity of rapid RT-PCR and standard laboratory-based NAAT appear to be essentially equivalent. In contrast, the rapid isothermal NAATs evaluated were less sensitive than either rapid RT-PCR or standard laboratory based NAATs. We believe the 81% sensitivity estimate for rapid isothermal NAAT best reflects test performance because the composite reference standard used for this calculation is a higher quality of evidence. Regardless of the sensitivity differences across methodologies, rapid isothermal NAAT will likely continue to be used due to test kit supply shortages affecting a variety of different test manufacturers. Also, compared to rapid RT-PCR which usually takes 45-60 minutes, rapid isothermal NAAT can generate results within 5-15 minutes, which is advantageous in many clinical settings. When using rapid isothermal tests, false negative results are reduced when testing is performed in low prevalence populations (1%). Conversely, a negative rapid isothermal test result in an individual with a high clinical suspicion of SARS-CoV-2 infection in a low prevalence area or anyone in a moderate (10%) or high prevalence (40%) population should be confirmed with a standard NAAT or rapid RT-PCR test when testing is available and the results will affect patient management.

Future research should include rigorously designed studies in symptomatic patients using specimen types that optimize the performance of the tests studied, with particular attention to time of testing in relationship to symptom onset. Studies of rapid isothermal methods other than Abbot ID NOW are also needed, as are comparative studies on the test performance of rapid and standard NAAT in asymptomatic individuals and children.

Table 7. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 1%, 10%, and 40% for rapid RT-PCR and standard non-rapid laboratory-based NAAT vs. composite reference standard

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

Outcome	**No of patients (studies)**	**Effect per 1,000 patients tested**						**Test accuracy CoE**
		Pre-test probability of 1%		**Pre-test probability of 10%**		**Pre-test probability of 40%**		
		Rapid RT-PCR	**Standard NAAT**	**Rapid RT-PCR**	**Standard NAAT**	**Rapid RT-PCR**	**Standard NAAT**	
True positives (patients with SARS-CoV2 infection)	460 (4)	10 (10 to 10)	10 (10 to 10)	98 (95 to 100)	98 (95 to 99)	392 (380 to 400)	392 (380 to 396)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having SARS-CoV2 infection)		0 (0 to 0)	0 (0 to 0)	2 (0 to 5)	2 (1 to 5)	8 (0 to 20)	8 (4 to 20)	
True negatives (patients without SARS-CoV2 infection)	329 (4)	960 (881 to 980)	960 (911 to 980)	873 (801 to 891)	873 (828 to 891)	582 (534 to 594)	582 (552 to 594)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having SARS-CoV2 infection)		30 (10 to 109)	30 (10 to 79)	27 (9 to 99)	27 (9 to 72)	18 (6 to 66)	18 (6 to 48)	

CoE: Certainty of evidence

Table 8. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 1%, 10%, and 40% for rapid isothermal NAAT and standard non-rapid laboratory-based NAAT vs. composite reference standard

	Rapid isothermal NAAT	Standard laboratory based NAAT
Sensitivity	0.81 (95% CI: 0.75 to 0.86)	0.99 (95% CI: 0.97 to 1.00)
Specificity	0.99.(95% CI: 0.96 to 1.00)	0.97 (95% CI: 0.93 to 0.99)

Outcome	**No of patients (studies)**	**Effect per 1,000 patients tested**						**Test accuracy CoE**
		Pre-test probability of 1%		**Pre-test probability of 10%**		**Pre-test probability of 40%**		
		Rapid isothermal NAAT	**Standard NAAT**	**Rapid isothermal NAAT**	**Standard NAAT**	**Rapid isothermal NAAT**	**Standard NAAT**	
True positives (patients with SARS-CoV-2 infection)	576 (4)	8 (8 to 9)	10 (10 to 10)	81 (75 to 86)	99 (97 to 100)	324 (300 to 344)	8 (8 to 9)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having SARS-CoV-2 infection)		2 (1 to 2)	0 (0 to 0)	19 (14 to 25)	1 (0 to 3)	76 (56 to 100)	2 (1 to 2)	
True negatives (patients without SARS-CoV-2 infection)	418 (4)	980 (950 to 990)	960 (921 to 980)	891 (864 to 900)	873 (837 to 891)	594 (576 to 600)	980 (950 to 990)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly		10 (0 to 40)	30 (10 to 69)	9 (0 to 36)	27 (9 to 63)	6 (0 to 24)	10 (0 to 40)	

classified as having SARS-CoV-2 infection)								
False positives (patients incorrectly classified as having SARS-CoV-2 infection)		10 (0 to 40)	30 (10 to 69)	9 (0 to 36)	27 (9 to 63)	6 (0 to 24)	10 (0 to 40)	

CoE: Certainty of evidence

RNA Testing in Exposed Individuals (Asymptomatic)

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 [89-91], 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 [89, 92, 93], a nursing home outbreak [94], active surveillance of passengers quarantined on a cruise ship or passengers of repatriation flights [95], hospital employees with close contact to COVID-19 positive patients [96], and customers and employees of a restaurant that had a COVID-19 outbreak [97]. 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 9** 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. In addition, the CDC has recently updated their guidance to allow for a reduced duration of post-exposure quarantine. Shorter quarantine can help reduce economic hardship and lessen stress on the public health system but may not capture the incubation period for all individuals. Per CDC guidance, quarantine can now end on day seven after last exposure when an individual remains asymptomatic and has a negative test [98]. 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. Some individuals may still be in the incubation phase, subsequently develop active viral shedding, and incorrectly consider themselves non-infected. 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% and 95% [57, 58, 62, 64, 65, 99], 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 [100]. 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-CoV-2 has been determined to be five days [101]. Thus, testing five days following exposure may be a reasonable time frame to consider post-exposure testing and would allow time to obtain test results for discontinuation of quarantine as early as day seven post-exposure. 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 [102].

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

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**
	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)		

CoE: Certainty of evidence

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.

RNA Testing in Unexposed, Hospitalized Individuals (Asymptomatic)

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 suggests 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 ³10%.
  - 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 [90, 91], 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% [25, 103, 104]. 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 1,000 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% [57, 58, 62, 64, 65, 99],

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, is changing over time, 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.

RNA Testing in Immunocompromised Individuals (Asymptomatic)

Recommendation 11: The IDSA panel recommends 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)*.

- **Remark**: This recommendation defines immunosuppressive procedures as cytotoxic chemotherapy, solid organ or stem cell transplantation, 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 hematopoietic stem cell (HSCT) or solid organ transplantation (SOT) regardless of a known exposure to COVID-19 *(strong recommendation, very low certainty of evidence)*.

- **Remark:** Testing should ideally be performed as close to the planned treatment/procedure as possible (e.g., within 48-72 hours).

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 transplantation or admission to the hospital. In addition, we were unable to evaluate the risks of delaying necessary transplants if testing was positive or not available and quarantine/delay of treatment was then required. A number of other professional societies have issued guidelines for HSCT or SOT candidates [105-108]. All current guidance recommends molecular diagnostic testing for SARS-CoV-2 shortly before transplantation [105-108]. If the results are positive, deferral is generally recommended. Recommendations 11 and 12 are paradigmatic situations for a strong recommendation, based on low certainty evidence, in order to avoid a potentially catastrophic event.

Benefits and harms

The panel considered that patients who will receive a transplant could suffer catastrophic outcomes if they have undiagnosed SARS-CoV-2 infection; hence, the strong recommendation in the setting of very low certainty evidence. The potential of nosocomial transmission of disease from an asymptomatic individual admitted to an inpatient ward of high-risk patients could also result in serious disease with poor outcomes. Although data are limited, there are reports documenting outbreaks of respiratory viruses in hospitalized immunocompromised hosts [109]. In addition, increased risks of severe adverse respiratory virus-related outcomes in this population are documented [110].

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. We did not identify any test accuracy studies directly assessing the performance of NAAT in asymptomatic individuals or immunocompromised hosts. However, based on existing evidence supporting that asymptomatic or pre-symptomatic patients may have similar virus loads and shedding as those who are symptomatic [90, 91], the panel agreed that test accuracy data from symptomatic patients would apply to asymptomatic transplant candidates being hospitalized.

Conclusions and research needs for this recommendation

The limited data available indicates that heavily immunocompromised patients have increased risk of severe outcomes from COVID-19 disease. Therefore, testing asymptomatic patients at the time of hospital admission and/or before transplantation is warranted (e.g., testing within 48 hours). In addition, transplant candidates should be screened with a standardized questionnaire for symptoms and known exposures in between visits as well as before transplant.

Although case reports of COVID-19 disease in transplant recipients are accumulating, more information is needed. One important question to address is the safety of transplantation in COVID-19 recovered patients. This group of patients includes individuals whose symptoms have resolved, are typically more than 21 days post-SARS-CoV-2 diagnosis [111], but continue to have RNA detected in respiratory secretions by sensitive NAAT methods. Research on alternative methods of viral detection (e.g., subgenomic RNA) as a predictor of ongoing viral replication, longitudinal follow-up of RNA shedding, assessments of the potential for relapsed infection and general clinical outcomes in transplant 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.

RNA Testing Before Immunosuppressive Therapy for Cancer (Asymptomatic)

Recommendation 13: The IDSA panel makes no recommendations for or against SARS-CoV-2 RNA testing before initiating immunosuppressive therapy in asymptomatic individuals with cancer *(evidence gap)*.

- **Remarks**:
  - The decision to pursue testing should be individualized. Factors to consider include the type of cancer, the need for induction *versus* maintenance immunosuppressive therapy, the type of immunosuppressive therapy, patient comorbidities and the availability of testing.
  - This recommendation does not apply to hematopoietic stem cell transplant candidates or recipients.

Summary of methods and results

This literature review focused on patients with hematologic or solid tumor malignancies and excluded studies specifically focused on hematopoietic transplant candidates/recipients. We did not identify any study that assessed the impact of SARS-CoV-2 NAAT prior to starting cancer treatment. There were also no studies directly comparing COVID-19 outcomes in cancer patients receiving treatment to cancer patients not receiving treatment. We identified 11 studies that compared the outcomes of COVID-19 between cancer patients and patients without cancer [112-122] and 22 studies that reported the outcomes of COVID-19 in cancer patients [43, 123-143] (**Tables s4i and s4j**). Fourteen [123, 124, 128-133, 135-137, 141-143] of the outcome studies included regression analyses to look for predictors of mortality and poor outcomes among cancer patients; however, they were not consistent in terms of the variables adjusted for in the models. Additionally, cancer treatment status, cancer stage, and comorbidities were not included in the final multivariable analysis in many of the models.

Overall, the evidence identified was of very low quality. Important limitations in the published literature include the observational nature of the studies, risk of bias due to selection bias and confounding, inconsistency in results and indirectness. Indirectness was due to lack of direct assessments of the effect of SARS-CoV-2 testing before initiation of immunosuppressive therapy and absence of comparisons of COVID-19 outcomes in cancer patients who either were or were not receiving immunosuppressive treatment.

Studies comparing COVID-19 outcomes in patients with cancer to those without cancer

Of the 11 studies that reported COVID-19 related outcomes in patients with cancer compared to those without cancer, four were focused on hematological malignancies [114, 118, 119, 122], one on solid malignancy [116] and six did not specify the type of malignancy [112, 113, 115, 117, 120, 121]. The studies of patient with hematological malignancies showed a possible increase in the risk of poor outcomes, such as death and ICU admission, when compared to patients without cancer. The single study that focused specifically on solid

malignancies showed a comparable mortality rate across groups; but when patients were stratified based on age, outcomes of COVID-19 cancer patients younger than 50 were worse than age-matched controls without cancer. Of note, the number of patients and events was small, raising concerns regarding imprecision as well as risk of bias. The studies that did not specify the type of malignancy showed variable results, with some observing comparable outcomes and others showing worse outcomes in cancer patients compared to patients without cancer. Some of the studies in this group conducted regression models to assess predictors of poor outcomes, but these methods were not consistent in terms of variables included in the models. When the presence of cancer was included in the multivariable models, many studies showed a trend toward worse outcomes, although the confidence intervals crossed the line of no difference in most of models [113, 115, 119].

Studies evaluating COVID-19 outcomes among patients with cancer

Of the 22 studies that reported outcomes of COVID-19 in cancer patients, seven focused on hematological malignancies [43, 123, 125, 126, 128, 132, 135], three on solid malignancy [127, 139, 143] and 12 did not specify the type of malignancy [124, 129-131, 133, 134, 136-138, 140-142]. The seven studies of hematological malignancy included three that were focused on plasma cell disorders [43, 125, 126] and four that did not specify the type of hematological malignancy [123, 128, 132, 135]. Study sample sizes and all-cause mortality rates varied across studies, as shown in **Table 10**. A single study evaluated the outcomes of hospitalized cancer patients who presented with symptoms suspicious of COVID-19 found that a positive SARS-CoV-2 PCR was associated with increased risk of mortality (OR 1.92) compared to a negative SARS-CoV-2 PCR in univariable analysis; however, it did not meet the threshold of statistical significance to be included in the multivariable model [124].

Table 10. Summary of Studies assessing all-cause Mortality in Cancer Patients with COVID-19

Malignancy	Study size Total number of subjects (N) (Range; median)	All-cause Mortality % Range (median)
Plasma cell disorders (3 studies)	N= 99 (20-56; 21)	0-35% (12%)
Non-specified heme malignancy (4 studies)	N= 232 (35-536; 134)	36-40% (37%)
Solid malignancy (3 studies)	N= 839 (4-200; 28)	25-33% (29%)
Malignancy type not specified (12 studies)	N= 4,315 (18-928; 211)	10-34% (23%)

Studies assessing the effect of cancer type, disease stage and treatment type on outcomes in patients with COVID-19

We identified 14 studies that reported multivariable regression models assessing the effect of cancer and its treatment on COVID-19 outcomes [123, 124, 128-133, 135-137, 141-143]. Two studies limited to COVID-19 patients with hematological malignancies reported results of multivariable regression models assessing predictors of mortality. One showed increased mortality in patients receiving chemotherapy [132], while the other showed an increased risk of death in patients with progressive malignancy and different types of hematological malignancies, but no association with time since cancer diagnosis or last treatment [135]. An additional study limited to solid malignancies showed an association between severe events and receipt of antitumor therapy within 14 days in a multivariable model [143]. The remaining 11 studies included cancer patients regardless of the type of cancer. Of these, four studies assessed the association between anti-cancer treatment (not otherwise specified) and mortality; three showed an increased risk of death [130, 136, 142] while the fourth study showed a decreased risk [137].

Six additional studies assessed the association between chemotherapy and outcomes. Four of the chemotherapy-focused studies observed an increased risk of death in patients

receiving treatment [121, 130, 131, 141]. The remaining two studies had conflicting results with one showing increased risk of poor outcomes [133] and other one showing decreased risk of poor outcomes [129]. Hormonal therapy, immunotherapy and targeted therapy were associated with lower risk of death in one study [131], while two others showed increased risk of mortality in patients receiving immune therapy and/or targeted therapy [121, 138]. Patients with a recent diagnosis of malignancy tended to have a lower risk of mortality in one study [117]. Having active malignancy was associated with higher mortality in one study [137] and remission was associated with less poor outcomes in another study [129]. Similarly, risk of mortality was increased in patients with progressing malignancy as well as stable/responding malignancy compared to patients who were in remission [130]. As for the disease stage and the presence of metastases, they were associated with increased mortality and poor outcomes in three studies [117, 121, 136]; however, one showed less poor outcomes in patients with metastatic disease [138]. Patients with hematological malignancies tended to have a higher risk of mortality and poor outcomes [129, 130, 138]. Finally, having intrathoracic or pulmonary malignancies was associated with increased risk of mortality in one study [129] but decreased mortality in another study [117].

Benefits and harms

The potential benefits of SARS CoV-2 testing before initiation of cancer treatment include the ability to identify patients with asymptomatic or pre-symptomatic infection and then potentially delaying or adjusting treatment depending on an individual's risk for a poor outcome from COVID-19 weighed against the deleterious effect of delayed or interrupted cancer treatment. This may be particularly important when cytotoxic chemotherapy or other treatments that have major effects on protective immunity are planned. However, depending on the type and stage of the underlying malignancy, delaying cancer therapy may not be possible even if SARS-CoV-2 infection is detected. In this case, identification of asymptomatic or pre-symptomatic infection may still be useful because it has potential implications for SARS-CoV-2 treatment and infection control practices as well as for anticipation of potential complications and patient education.

The potential harms of testing include obtaining false positives results, especially when the prevalence of SARS-CoV-2 infection in the community is low. False positives may unnecessarily delay critical treatment of the underlying malignancy. False positives may also promote anxiety, and result in unneeded treatment for COVID-19 as well as unnecessary contact tracing related to the inaccurate diagnosis. True positive results may also lead to unnecessarily delayed or altered treatment, which may be harmful if certain cancer treatments (i.e., non-cytotoxic or less immunosuppressive therapies) do not substantially increase the risk of poor COVID-19 related outcomes.

Additional considerations

Hematologic and solid tumor malignancies are a diverse group of complex diseases. Current chemotherapeutic agents and biologic response modifiers used to treat cancer have variable effects on the immune system. Some, but not all, cancer treatment regimens are associated with an increased risk for developing infection, while other drugs might actually have protective effects. In the case of SARS-CoV-2 infection, limited data in the form of case reports suggests that receipt of Bruton tyrosine kinase inhibitors might be associated with less severe SARS-CoV-2 infection [144, 145]. It has also been speculated that immune checkpoint inhibitors could reduce the severity of COVID-19 complications. A single population-based study reported that receipt of androgen receptor signaling antagonists for prostate cancer was associated with a lower risk for acquiring SARS-CoV-2 infection [146]. Additional considerations related to the decision to perform nucleic acid amplification testing in asymptomatic cancer patients are the prevalence of infection in the community, the availability of testing and turn-around-time to test results.

Conclusions and research needs for this recommendation

In summary, most cancer studies reported poor outcomes in COVID-19 patients receiving cytotoxic chemotherapy as well as in those with active or progressive disease and/or hematological malignancies. Evidence linking recent oncologic therapy to COVID-19 complications was, however, mixed. Significant heterogeneity across study populations and

statistical analyses precluded making generalized conclusions about the impact of cancer type, disease stage and treatment type on patient outcomes. The number of patients and/or events was small in many of the models, which also raises concerns about imprecision. Most confidence intervals crossed the threshold of no difference. Furthermore, the factors adjusted for in different models varied widely and the selection for inclusion of variables in the models was dependent on findings of univariable analyses, which raise additional concerns about over-fitting combined with the effect of unknown confounders and excluded variables.

Going forward, interventional studies comparing testing *versus* no testing before initiation or continuation of immunosuppressive treatment are unlikely to be feasible. Thus, decisions about testing before initiation of oncologic treatment should be individualized and consider the availability of testing and whether the results would affect patient management decisions. Factors to consider include the urgency and type of treatment, underlying medical conditions and turn-around-time to SARS-CoV-2 NAAT results. Standardized symptom screens and queries regarding known contacts with laboratory confirmed cases are also useful to help guide targeted testing. To understand the potential impact of immunosuppressive therapies on COVID-19 outcomes, observational registries should ideally be prospective and enroll patients across a spectrum of infection severity and treatment modalities. Case-control studies that include well-matched controls could also be valuable for assessing the impact of different cancer therapies or diagnoses on patient outcomes.

RNA Testing Before Immunosuppressive Therapy in Individuals with Autoimmune Disease (Asymptomatic)

Recommendation 14: The IDSA panel makes no recommendations for or against SARS-CoV-2 RNA testing before the initiation of immunosuppressive therapy in asymptomatic individuals with autoimmune disease *(evidence gap)*.

- **Remark**: The decision to pursue testing should be individualized. Factors that may affect the decision to test include the type and severity of autoimmune disease, the type of immunosuppressive therapy, the need for induction *versus* maintenance immunosuppressive therapy, patient comorbidities and the feasibility of testing.

Summary of methods and results

We could not identify any studies that assessed the impact of SARS-CoV-2 nucleic acid amplification testing before initiation of immunosuppressive therapy for autoimmune disease on patient outcomes. Specifically, we searched for studies in which testing was performed prior to starting immunosuppressive therapy as treatment for rheumatologic, inflammatory bowel, dermatologic or neurologic autoimmune conditions. There was also a lack of studies directly comparing COVID-19 outcomes in patients with autoimmune disease on immunosuppressive therapy versus not receiving immunosuppressive therapy.

We did identify 33 studies (**Tables s4k and s4l**) that assessed the prevalence and outcomes of COVID-19 in patients with autoimmune conditions, including 15 studies of patients with rheumatologic disease [147-161], five studies of patients with dermatologic disease [162-166], two studies of patients with neurologic disease [167, 168], and 11 studies of patients with inflammatory bowel disease [169-179]. Some conducted regression analyses to assess the association between immunosuppressive therapy and COVID-19 outcomes, but reports were not consistent in terms of adjusting for other confounding variables [160, 161, 166, 172, 179]. The overall quality of the evidence was very low due to the observational nature of the identified studies, high risk of bias (mostly due to high risk of selection bias), inconsistent results among different studies and indirect comparisons.

Rheumatologic disease review

The prevalence of SARS-CoV-2 infection in the seven studies of patients with rheumatologic disease ranged from 0.2 to 47.2% (median 0.8%). The rate of hospitalization

ranged from 58.5-70.0% (median 68.8%, four studies), with an intensive care admission rate of 3.4-9.8% (median 5.9%, three studies), and a death rate of 0.0-26.3% (median 9.8%, seven studies). We identified three retrospective cohort studies that compared outcomes of COVID-19 in patients with and without rheumatologic diseases, and in patients on and off treatment for rheumatologic diseases [150, 160, 161]. Overall, there was no association between the presence of rheumatologic diseases, or their treatments, and poor outcomes in patients with COVID-19.

Inflammatory bowel disease review

The prevalence of SARS-CoV-2 infection in seven studies of patients with inflammatory bowel disease ranged from 0.0 to 3.0% (median 0.3%). The rate of hospitalization ranged from 26.6-66% (median 33.3%, seven studies), with an intensive care admission rate of 0.0-8.3% (median 3.6%, seven studies), and a death rate of 0.0-20.0% (median 5.0%, seven studies). We identified one retrospective cohort study that compared outcomes of COVID-19 in patients with and without inflammatory bowel disease [179]. It showed no association between the presence of inflammatory bowel disease and poor outcomes in patients with COVID-19. However, the correlation with specific treatment options or immunosuppression was unclear.

Dermatologic disease review

The prevalence of SARS-CoV-2 infection in the three studies of patients with autoimmune dermatologic disease ranged from 0.8 to 3.6% (median 1.1%). The hospitalization rate ranged from 20.0-66.7% (median 41.7%, three studies), with an intensive care admission rate of 16.7-33.3% (two studies), and a death rate of 0.0% (95% CI 0.0-26.5%; one study including 12 patients). We identified one retrospective cohort study that compared the prevalence and outcomes of COVID-19 in patients with plaque psoriasis on biologics to the population of the Lombardi region in Italy. Although univariable analysis showed an increased risk of COVID-19 in patients on biologics compared to the population, there was no association with intensive care admission or death [166].

Neurologic disease review

The prevalence of SARS-CoV-2 infection in the one study of patients with autoimmune neurologic disease was 0.04% (95% CI 0.0-0.15%; 4,864 patients). The hospitalization rate was 23.7% (95% CI 14.7-34.8; one study including 76 patients), and the death rate ranged from 0.0-7.8% (two studies). We could not identify any studies that reported intensive care admission rates or compared outcomes COVID-19 in patients with and without autoimmune neurologic disease.

Benefits and harms

The potential benefits of SARS CoV-2 testing before initiation of biologic therapy is the ability to identify asymptomatic or pre-symptomatic infection. Knowing a patient's SARS-CoV-2 infection status could inform treatment delay or adjustments depending on an individual's risk for poor outcomes from COVID-19 (particularly when medications that have major effects on cell immunity are planned) *versus* the deleterious effect of delayed or interrupted therapy for autoimmune disease. Identification of asymptomatic or pre-symptomatic infections also has potential implications for patient self-isolation recommendations, contact tracing and treatment. The potential harms of testing include obtaining false positives results, especially when the prevalence of SARS-CoV-2 infection in the community is low. False positives may lead to unnecessary delays in treatment, unnecessary treatment for SARS-CoV-2, and anxiety related to an (inaccurate) diagnosis of SARS-CoV-2. True positive results may also lead to unnecessarily delayed or altered anti-inflammatory therapy, if it turns out that treatment of infected patients does not increase risk of adverse COVID-19 outcomes.

Additional considerations

Biologic response modifiers are a diverse group of drugs with different mechanisms of action and variable effects on the immune system. Some, but not all, have been associated with an increased risk for developing infection including respiratory virus infections [180]. In contrast, several biologic agents including IL-6 and IL-1 inhibitors, as well as various Janus kinase (JAK) inhibitors, are currently being studied as treatments for the inflammatory response associated with COVID-19. Questions have been raised about whether these drugs may actually

reduce the risk for severe SARS-CoV-2 inflammatory effects in patients who are already receiving them for treatment of autoimmune disease. Additional considerations related to the decision to perform NAAT in asymptomatic patients is the prevalence of infection in the community, the availability of testing and turn-around-time to test results.

Conclusions and research needs for this recommendation

Currently, there is no evidence that patients with autoimmune disease or those receiving immunosuppressive biologic drugs are at an increased risk for becoming infected with SARS-CoV-2. However, there is theoretical concern that patients with SARS-CoV-2 infection who receive immunosuppressive treatment will be at increased risk of more severe COVID-19 disease, especially if they also have other underlying comorbidities and/or older age which predispose to worse outcomes. Concomitant chronic steroid use ($\geq$10 mg a day) may be a risk for poor COVID-19 outcomes, but this was not reproducibly observed across all studies. Interventional studies comparing nucleic acid amplification testing *versus* no testing before initiation or continuation of biologic therapy are unlikely to be feasible. Therefore, decisions as to whether to test before initiation of immunosuppressive therapy should be individualized and include an assessment of whether or not the results would change patient management decisions. Factors to consider include the urgency and type of treatment, underlying medical conditions and availability of SARS-CoV-2 NAATs. Standardized symptom screens and queries regarding known contacts with laboratory confirmed cases are also useful to help guide targeted testing. To understand the potential impact of immunosuppressive drugs on COVID-19 outcomes, observational registries should ideally be prospective, include larger numbers of patients across a spectrum of infection severity and evaluate clinically important outcomes. Case-control designs could include well-matched controls without autoimmune disease as well as studies evaluating specific groups of patients who are either receiving or not receiving common treatments for autoimmune disease.

RNA Testing in Unexposed Individuals Undergoing Major Time-Sensitive Surgeries or Aerosol-Generating Procedures (Asymptomatic)

Recommendation 15: The IDSA panel suggests 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 16: 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 11**.

Recommendation 17: 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)*.

- **Remarks**:
  - 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 11**.
  - 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 [25, 103, 104]. 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 very 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 [181]. 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 [181]. 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 three 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 [182]. 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 11. Various Organizations' Lists of Aerosol-Generating Procedures*

	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 • Bronchoscopy	• Aspiration of respiratory tract • Intubation • Resuscitation • Bronchoscopy • Autopsy

CDC: Centers for Disease Control and Prevention; **WHO**: World Health Organization; **BiPAP**: bilevel positive airway pressure; **CPAP**: continuous positive airway pressure

*Accessed April 16, 2020

References

1. Centers for Disease Control and Prevention. Health care Infection Prevention and Control FAQs for COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-faq.html.
2. Centers for Disease Control and Prevention. Prevention Strategies for Seasonal Influenza in Health care Settings. Available at: https://www.cdc.gov/flu/professionals/infectioncontrol/health_caresettings.htm.
3. World Health Organization. Advice on the use of masks in the context of COVID-19. Available at: https://www.who.int/publications-detail/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-health_care-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak.
4. World Health Organization. Epidemic- and pandemic-prone acute respiratory diseases - Infection prevention and control in health care. Available at: https://www.who.int/csr/resources/publications/aidememoireepidemicpandemid/en/.

Narrative Summaries of Diagnostics Undergoing Evaluation

SARS-CoV-2 antigen detection tests have recently become available. We anticipate systematically reviewing the clinical utility of these tests as data accumulates on their performance in comparison to NAAT. In addition, current NAATs detect genomic viral RNA but cannot distinguish infectious from non-infectious virus. This determination typically requires viral culture, which is not routinely performed in clinical laboratories for biosafety reasons and is likely less sensitive than NAAT. A number of investigators have described the use of assays designed to detect subgenomic RNA (sgRNA), which may be used in addition to standard NAATs targeting genomic RNA [183, 184]. The detection of sgRNA is thought to represent active viral replication and could be a surrogate for culture positivity. However, additional studies are required to determine the correlation between sgRNA detection and culture. Whether individuals who remain sgRNA positive after symptom resolution, and potentially seroconversion, remain infectious to others also is not known. Lastly, mRNA vaccines designed that encode the SARS-CoV-2 spike protein have received emergency use authorization. There is currently no evidence that receipt of the vaccine would interfere with SARS-CoV-2 molecular diagnostic testing.

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 United States was hampered by limited test availability early in the outbreak, there are now more than 180 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 transplantation.

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 [61, 90, 185]. 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 [64, 186]. 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 [90, 91]. 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 [187].

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 depends 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. 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 12**

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 diseases 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 13** 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 12. 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

URI: upper respiratory infection; **ILI**: influenza-like illness; **LRTI**: lower respiratory tract infection

Table 13. 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 two different NAATs (one of the two may be the index test)
OPTION 3	Dual positive results from a single NAAT targeting two 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.

Notes

Acknowledgement

The expert panel thanks the Infectious Diseases Society of America for supporting guideline development, and specifically the Executive Committee of the IDSA Board of Directors as well as IDSA staff members Dana Wollins, Genet Demisashi, and Rebecca Goldwater for their continued support throughout the guideline process. The panel also expresses its appreciation to the members of SHEA, PIDS, and ASM who provided their thoughtful and comprehensive review.

Financial Support

This project was funded in part by a cooperative agreement with the Centers for Disease Control and Prevention (CDC) (grant number 6 NU50CK000477-04-01). The CDC is an agency within the Department of Health and Human Services (HHS). The contents of this guideline do not necessarily represent the policy of CDC or HHS and should not be considered an endorsement by the Federal Government.

COI Summary

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

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

the Society for Vascular Surgery, and The American Society of Hematology and is a Board member for the Evidence Foundation. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England journal of medicine **2020**; 382(8): 727-33.
2. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet **2020**; 395(10224): 565-74.
3. Gorbalenya AE, Baker SC, Baric RS, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nature Microbiology **2020**; 5(4): 536-44.
4. World Health Organization. Rolling updates on coronavirus disease (COVID-19). Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen. Accessed 30 April 2020.
5. U.S. Food and Drug Administration. Coronavirus Disease In Vitro Diagnostics EUAs. Available at: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd. Accessed 30 April 2020.
6. Morgan RL, Florez I, Falavigna M, et al. Development of rapid guidelines: 3. GIN-McMaster Guideline Development Checklist extension for rapid recommendations. Health Res Policy Syst **2018**; 16(1): 63.
7. Hanson KE, Caliendo AM, Arias CA, et al. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19:Serologic Testing. Clin Infect Dis **2020**.
8. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol **2011**; 64(4): 395-400.
9. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol **2005**; 58(10): 982-90.
10. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med **2010**; 29(29): 3046-67.
11. Doebler P. mada: Meta-Analysis of Diagnostic Accuracy. R package 0.5.10. ed, **2020**.
12. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health **2019**; 22(4): 153-60.
13. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. . **2020**.
14. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med **2011**; 155(8): 529-36.
15. Schünemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 21 part 1. Study design, risk of bias, and indirectness in rating the certainty across a body of evidence for test accuracy. J Clin Epidemiol **2020**; 122: 129-41.
16. Schünemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 21 part 2. Test accuracy: inconsistency, imprecision, publication bias, and other domains for rating the certainty of evidence and presenting it in evidence profiles and summary of findings tables. J Clin Epidemiol **2020**; 122: 142-52.

17. Ai J-W, Zhang H-C, Xu T, et al. Optimizing diagnostic strategy for novel coronavirus pneumonia, a multi-center study in Eastern China. **2020**: 2020.02.13.20022673.
18. Alexander PE, Bero L, Montori VM, et al. World Health Organization recommendations are often strong based on low confidence in effect estimates. J Clin Epidemiol **2014**; 67(6): 629-34.
19. Guyatt GH, Alonso-Coello P, Schünemann HJ, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol **2016**; 80: 3-7.
20. Bordi L, Nicastri E, Scorzolini L, et al. Differential diagnosis of illness in patients under investigation for the novel coronavirus (SARS-CoV-2), Italy, February 2020. Euro Surveill **2020**; 25(8).
21. Hsih WH, Cheng MY, Ho MW, et al. Featuring COVID-19 cases via screening symptomatic patients with epidemiologic link during flu season in a medical center of central Taiwan. J Microbiol Immunol Infect **2020**.
22. Liu R, Han H, Liu F, et al. Positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 cases from one hospital in Wuhan, China, from Jan to Feb 2020. Clin Chim Acta **2020**; 505: 172-5.
23. Tolia VM, Chan TC, Castillo EM. Preliminary Results of Initial Testing for Coronavirus (COVID-19) in the Emergency Department. The western journal of emergency medicine **2020**.
24. Pu H, Xu Y, Doig GS, Zhou Y. Screening and managing of suspected or confirmed novel coronavirus (COVID-19) patients: experiences from a tertiary hospital outside Hubei province. **2020**: 2020.03.20.20038679.
25. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic Population. **2020**.
26. Huang G, Zeng W, Wang W, et al. Triaging patients in the outbreak of the 2019 novel coronavirus. **2020**: 2020.03.13.20035212.
27. Infectious Diseases Society of America. COVID-19 Prioritization of Diagnostic Testing. Available at: https://www.idsociety.org/globalassets/idsa/public-health/covid-19-prioritization-of-dx-testing.pdf. Accessed 30 April 2020.
28. Centers for Disease Control and Prevention. Priorities for testing patients with suspected COVID-19 infection. Available at: https://www.cdc.gov/coronavirus/2019-ncov/downloads/priority-testing-patients.pdf. Accessed 30 April 2020.
29. Azzi L, Baj A, Alberio T, et al. Rapid Salivary Test suitable for a mass screening program to detect SARS-CoV-2: A diagnostic accuracy study. J Infect **2020**; 81(3): e75-e8.
30. Hanson KE, Barker AP, Hillyard DR, et al. Self-Collected Anterior Nasal and Saliva Specimens versus Healthcare Worker-Collected Nasopharyngeal Swabs for the Molecular Detection of SARS-CoV-2. J Clin Microbiol **2020**.
31. Iwasaki S, Fujisawa S, Nakakubo S, et al. Comparison of SARS-CoV-2 detection in nasopharyngeal swab and saliva. J Infect **2020**; 81(2): e145-e7.
32. Landry ML, Criscuolo J, Peaper DR. Challenges in use of saliva for detection of SARS CoV-2 RNA in symptomatic outpatients. J Clin Virol **2020**; 130: 104567.
33. Leung EC, Chow VC, Lee MK, Lai RW. Deep throat saliva as an alternative diagnostic specimen type for the detection of SARS-CoV-2. J Med Virol **2020**.

34. McCormick-Baw C, Morgan K, Gaffney D, et al. Saliva as an Alternate Specimen Source for Detection of SARS-CoV-2 in Symptomatic Patients Using Cepheid Xpert Xpress SARS-CoV-2. J Clin Microbiol **2020**; 58(8).
35. McCulloch DJ, Kim AE, Wilcox NC, et al. Comparison of Unsupervised Home Self-collected Midnasal Swabs With Clinician-Collected Nasopharyngeal Swabs for Detection of SARS-CoV-2 Infection. JAMA Netw Open **2020**; 3(7): e2016382.
36. Migueres M, Mengelle C, Dimeglio C, et al. Saliva sampling for diagnosing SARS-CoV-2 infections in symptomatic patients and asymptomatic carriers. J Clin Virol **2020**; 130: 104580.
37. Otto MP, Darles C, Valero E, Benner P, Dutasta F, Janvier F. Posterior oropharyngeal salivafor the detection of SARS-CoV-2. Clin Infect Dis **2020**.
38. Patel MR, Carroll D, Ussery E, et al. Performance of oropharyngeal swab testing compared to nasopharyngeal swab testing for diagnosis of COVID-19 -United States, January-February 2020. Clin Infect Dis **2020**.
39. Pham J, Meyer S, Nguyen C, et al. Performance Characteristics of a High-Throughput Automated Transcription-Mediated Amplification Test for SARS-CoV-2 Detection. J Clin Microbiol **2020**; 58(10).
40. Procop GW, Brock JE, Reineks EZ, et al. A Comparison of Five SARS-CoV-2 Molecular Assays With Clinical Correlations. Am J Clin Pathol **2020**.
41. Tu YP, Jennings R, Hart B, et al. Swabs Collected by Patients or Health Care Workers for SARS-CoV-2 Testing. The New England journal of medicine **2020**; 383(5): 494-6.
42. Vermeiren C, Marchand-Senécal X, Sheldrake E, et al. Comparison of Copan ESwab and FLOQSwab for COVID-19 Diagnosis: Working around a Supply Shortage. J Clin Microbiol **2020**; 58(6).
43. Wang X, Tan L, Wang X, et al. Comparison of nasopharyngeal and oropharyngeal swabs for SARS-CoV-2 detection in 353 patients received tests with both specimens simultaneously. Int J Infect Dis **2020**; 94: 107-9.
44. Williams E, Bond K, Zhang B, Putland M, Williamson DA. Saliva as a Noninvasive Specimen for Detection of SARS-CoV-2. J Clin Microbiol **2020**; 58(8).
45. Yokota I, Shane PY, Okada K, et al. Mass screening of asymptomatic persons for SARS-CoV-2 using saliva. Clin Infect Dis **2020**.
46. LeBlanc JJ, Heinstein C, MacDonald J, Pettipas J, Hatchette TF, Patriquin G. A combined oropharyngeal/nares swab is a suitable alternative to nasopharyngeal swabs for the detection of SARS-CoV-2. J Clin Virol **2020**; 128: 104442.
47. Pere H, Podglajen I, Wack M, et al. Nasal Swab Sampling for SARS-CoV-2: a Convenient Alternative in Times of Nasopharyngeal Swab Shortage. J Clin Microbiol **2020**; 58(6).
48. Vlek ALM, Wesselius TS, Achterberg R, Thijsen SFT. Combined throat/nasal swab sampling for SARS-CoV-2 is equivalent to nasopharyngeal sampling. Eur J Clin Microbiol Infect Dis **2020**.
49. Byrne RL, Kay GA, Kontogianni K, et al. Saliva Alternative to Upper Respiratory Swabs for SARS-CoV-2 Diagnosis. Emerg Infect Dis **2020**; 26(11).
50. Güçlü E, Koroglu M, Yürümez Y, et al. Comparison of saliva and oro-nasopharyngeal swab sample in the molecular diagnosis of COVID-19. Rev Assoc Med Bras (1992) **2020**; 66(8): 1116-21.

51. Lin C, Xiang J, Yan M, Li H, Huang S, Shen C. Comparison of throat swabs and sputum specimens for viral nucleic acid detection in 52 cases of novel coronavirus (SARS-Cov-2)-infected pneumonia (COVID-19). Clin Chem Lab Med **2020**; 58(7): 1089-94.
52. Moreno-Contreras J, Espinoza MA, Sandoval-Jaime C, et al. Saliva Sampling and Its Direct Lysis, an Excellent Option To Increase the Number of SARS-CoV-2 Diagnostic Tests in Settings with Supply Shortages. J Clin Microbiol **2020**; 58(10).
53. Pasomsub E, Watcharananan SP, Boonyawat K, et al. Saliva sample as a non-invasive specimen for the diagnosis of coronavirus disease 2019: a cross-sectional study. Clin Microbiol Infect **2020**.
54. Skolimowska K, Rayment M, Jones R, Madona P, Moore LSP, Randell P. Non-invasive saliva specimens for the diagnosis of COVID-19: caution in mild outpatient cohorts with low prevalence. Clin Microbiol Infect **2020**.
55. Vaz SN, Santana DS, Netto EM, et al. Saliva is a reliable, non-invasive specimen for SARS-CoV-2 detection. Braz J Infect Dis **2020**.
56. Wehrhahn MC, Robson J, Brown S, et al. Self-collection: An appropriate alternative during the SARS-CoV-2 pandemic. J Clin Virol **2020**; 128: 104417.
57. Tu Y-P, Jennings R, Hart B, et al. Patient-collected tongue, nasal, and mid-turbinate swabs for SARS-CoV-2 yield equivalent sensitivity to health care worker collected nasopharyngeal swabs. **2020**: 2020.04.01.20050005.
58. Wehrhahn MC, Robson J, Brown S, et al. Self-collection: an appropriate alternative during the SARS-CoV-2 pandemic. **2020**: 2020.04.09.20057901.
59. Kojima N, Turner F, Slepnev V, et al. Self-Collected Oral Fluid and Nasal Swabs Demonstrate Comparable Sensitivity to Clinician Collected Nasopharyngeal Swabs for Covid-19 Detection. **2020**: 2020.04.11.20062372.
60. Kim JY, Ko JH, Kim Y, et al. Viral Load Kinetics of SARS-CoV-2 Infection in First Two Patients in Korea. J Korean Med Sci **2020**; 35(7): e86.
61. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature **2020**.
62. Yang Y, Yang M, Yuan J, et al. Comparative Sensitivity of Different Respiratory Specimen Types for Molecular Diagnosis and Monitoring of SARS-CoV-2 Shedding. Innovation (N Y) **2020**; 1(3): 100061.
63. Gao Y, Yuan Y, Li TT, et al. Evaluation the auxiliary diagnosis value of antibodies assays for detection of novel coronavirus (SARS-Cov-2) causing an outbreak of pneumonia (COVID-19). medRxiv **2020**: 2020.03.26.20042044.
64. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA **2020**.
65. Yu F, Yan L, Wang N, et al. Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients. Clin Infect Dis **2020**.
66. Tan W, Lu Y, Zhang J, et al. Viral Kinetics and Antibody Responses in Patients with COVID-19. medRxiv **2020**: 2020.03.24.20042382.
67. Lin C, Xiang J, Yan M, Li H, Huang S, Shen C. Comparison of throat swabs and sputum specimens for viral nucleic acid detection in 52 cases of novel coronavirus (SARS-Cov-2) infected pneumonia (COVID-19). medRxiv **2020**: 2020.02.21.20026187.

68. Ai J, Gong J, Xing L, et al. Analysis of factors associated early diagnosis in coronavirus disease 2019 (COVID-19). **2020**: 2020.04.09.20059352.
69. Zhou F, Yu X, Tong X, Zhang R. Clinical features and outcomes of 197 adult discharged patients with COVID-19 in Yichang, Hubei. **2020**: 2020.03.26.20041426.
70. Bulterys PL, Garamani N, Stevens B, et al. Comparison of a laboratory-developed test targeting the envelope gene with three nucleic acid amplification tests for detection of SARS-CoV-2. J Clin Virol **2020**; 129: 104427.
71. Eckel F, Küsters F, Drossel B, Konert M, Mattes H, Schopf S. Variplex™ test system fails to reliably detect SARS-CoV-2 directly from respiratory samples without RNA extraction. Eur J Clin Microbiol Infect Dis **2020**; 39(12): 2373-7.
72. Harrington A, Cox B, Snowdon J, et al. Comparison of Abbott ID Now and Abbott m2000 Methods for the Detection of SARS-CoV-2 from Nasopharyngeal and Nasal Swabs from Symptomatic Patients. J Clin Microbiol **2020**; 58(8).
73. Hogan CA, Garamani N, Lee AS, et al. Comparison of the Accula SARS-CoV-2 Test with a Laboratory-Developed Assay for Detection of SARS-CoV-2 RNA in Clinical Nasopharyngeal Specimens. J Clin Microbiol **2020**; 58(8).
74. Hou H, Chen J, Wang Y, et al. Multicenter Evaluation of the Cepheid Xpert Xpress SARS-CoV-2 Assay for the Detection of SARS-CoV-2 in Oropharyngeal Swab Specimens. J Clin Microbiol **2020**; 58(8).
75. Lieberman JA, Pepper G, Naccache SN, Huang ML, Jerome KR, Greninger AL. Comparison of Commercially Available and Laboratory-Developed Assays for In Vitro Detection of SARS-CoV-2 in Clinical Laboratories. J Clin Microbiol **2020**; 58(8).
76. Liotti FM, Menchinelli G, Marchetti S, et al. Evaluating the newly developed BioFire COVID-19 test for SARS-CoV-2 molecular detection. Clin Microbiol Infect **2020**.
77. Loeffelholz MJ, Alland D, Butler-Wu SM, et al. Multicenter Evaluation of the Cepheid Xpert Xpress SARS-CoV-2 Test. J Clin Microbiol **2020**; 58(8).
78. McDonald S, Courtney DM, Clark AE, et al. Diagnostic Performance of a Rapid Point-of-care Test for SARS-CoV-2 in an Urban Emergency Department Setting. Acad Emerg Med **2020**.
79. Mitchell SL, George KS. Evaluation of the COVID19 ID NOW EUA assay. J Clin Virol **2020**; 128: 104429.
80. Moore NM, Li H, Schejbal D, Lindsley J, Hayden MK. Comparison of Two Commercial Molecular Tests and a Laboratory-Developed Modification of the CDC 2019-nCoV Reverse Transcriptase PCR Assay for the Detection of SARS-CoV-2. J Clin Microbiol **2020**; 58(8).
81. Moran A, Beavis KG, Matushek SM, et al. Detection of SARS-CoV-2 by Use of the Cepheid Xpert Xpress SARS-CoV-2 and Roche cobas SARS-CoV-2 Assays. J Clin Microbiol **2020**; 58(8).
82. Smith E, Zhen W, Manji R, Schron D, Duong S, Berry GJ. Analytical and Clinical Comparison of Three Nucleic Acid Amplification Tests for SARS-CoV-2 Detection. J Clin Microbiol **2020**; 58(9).
83. Smithgall MC, Scherberkova I, Whittier S, Green DA. Comparison of Cepheid Xpert Xpress and Abbott ID Now to Roche cobas for the Rapid Detection of SARS-CoV-2. J Clin Virol **2020**; 128: 104428.

84. Stevens B, Hogan CA, Sahoo MK, et al. Comparison of a Point-of-Care Assay and a High-Complexity Assay for Detection of SARS-CoV-2 RNA. J Appl Lab Med **2020**; 5(6): 1307-12.
85. Thwe PM, Ren P. How many are we missing with ID NOW COVID-19 assay using direct nasopharyngeal swabs? Findings from a mid-sized academic hospital clinical microbiology laboratory. Diagn Microbiol Infect Dis **2020**; 98(2): 115123.
86. Visseaux B, Le Hingrat Q, Collin G, et al. Evaluation of the QIAstat-Dx Respiratory SARS-CoV-2 Panel, the First Rapid Multiplex PCR Commercial Assay for SARS-CoV-2 Detection. J Clin Microbiol **2020**; 58(8).
87. Wolters F, van de Bovenkamp J, van den Bosch B, et al. Multi-center evaluation of cepheid xpert® xpress SARS-CoV-2 point-of-care test during the SARS-CoV-2 pandemic. J Clin Virol **2020**; 128: 104426.
88. Zhen W, Smith E, Manji R, Schron D, Berry GJ. Clinical Evaluation of Three Sample-to-Answer Platforms for Detection of SARS-CoV-2. J Clin Microbiol **2020**; 58(8).
89. Hu Z, Song C, Xu C, et al. Clinical Characteristics of 24 Asymptomatic Infections with COVID-19 Screened among Close Contacts in Nanjing, China. **2020**: 2020.02.20.20025619.
90. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. The New England journal of medicine **2020**; 382(12): 1177-9.
91. Danis K, Epaulard O, Benet T, et al. Cluster of coronavirus disease 2019 (Covid-19) in the French Alps, 2020. Clin Infect Dis **2020**; ciaa424.
92. Bi Q, Wu Y, Mei S, et al. Epidemiology and Transmission of COVID-19 in Shenzhen China: Analysis of 391 cases and 1,286 of their close contacts. **2020**: 2020.03.03.20028423.
93. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic Transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. MMWR Morbidity and mortality weekly report **2020**; 69(14): 411-5.
94. Kimball A, Hatfield K, Arons M, et al. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility — King County, Washington, March 2020. MMWR Morbidity and mortality weekly report **2020**; 69.
95. Gostic K, Gomez ACR, Mummah RO, Kucharski AJ, Lloyd-Smith JO. Estimated effectiveness of symptom and risk screening to prevent the spread of COVID-19. eLife **2020**; 9: e55570.
96. Folgueira MD, Munoz-Ruiperez C, Alonso-Lopez MA, Delgado R. SARS-CoV-2 infection in Health Care Workers in a large public hospital in Madrid, Spain, during March 2020. **2020**: 2020.04.07.20055723.
97. Jianyun L, Jieni G, Kuibiao L, et al. COVID-19 Outbreak Associated with Air Conditioning in Restaurant, Guangzhou, China, 2020. Emerging Infectious Disease journal **2020**; 26(7).
98. Centers for Disease Control and Prevention. When to Quarantine. Available at: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html. Accessed 6 December 2020.
99. Pere H, Podglajen I, Wack M, et al. Nasal swab sampling for SARS-CoV-2: A convenient alternative in time of nasopharyngeal swab shortage. J Clin Microbiol **2020**.
100. Centers for Disease Control and Prevention. Interim U.S. Guidance for Risk Assessment and Public Health Management of Healthcare Personnel with Potential Exposure in a Healthcare Setting to Patients with Coronavirus Disease 2019 (COVID-19). Available at:

https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html. Accessed 5 May 2020.

101. Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med **2020**.
102. Centers for Disease Control and Prevention. Infection Control Guidance for Healthcare Professionals about Coronavirus (COVID-19). Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control.html. Accessed 4 May 2020.
103. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. **2020**.
104. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in cancer patients of a tertiary hospital in Wuhan. **2020**: 2020.02.22.20025320.
105. Waghmare A, Abidi MZ, Boeckh M, et al. Guidelines for COVID-19 Management in Hematopoietic Cell Transplantation and Cellular Therapy Recipients. Biology of Blood and Marrow Transplantation **2020**; 26(11): 1983-94.
106. Panel C-TG. Special Considerations in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Therapy Candidates, Donors, and Recipients. National Institutes of Health, **2020**.
107. Ljungman P, Mikulska M, de la Camara R, et al. The challenge of COVID-19 and hematopoietic cell transplantation; EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. Bone Marrow Transplantation **2020**; 55(11): 2071-6.
108. American Society of Transplantation. Recommendations and Guidance for Organ Donor Testing. American Society of Transplantation, **2020**.
109. Abbas S, Raybould JE, Sastry S, de la Cruz O. Respiratory viruses in transplant recipients: more than just a cold. Clinical syndromes and infection prevention principles. Int J Infect Dis **2017**; 62: 86-93.
110. Pochon C, Voigt S. Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients. Frontiers in microbiology **2018**; 9: 3294.
111. Centers for Disease Control and Prevention. Discontinuation of Transmission-Based Precautions and Disposition of Patients with COVID-19 in Healthcare Settings (Interim Guidance). Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html. Accessed 6 December 2020.
112. Dai M, Liu D, Liu M, et al. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. Cancer Discov **2020**; 10(6): 783-91.
113. Gallo O, Locatello LG, Orlando P, et al. Cancer population may be paradoxically protected from severe manifestations of COVID-19. J Infect **2020**; 81(2): e156-e8.
114. He W, Chen L, Chen L, et al. COVID-19 in persons with haematological cancers. Leukemia **2020**; 34(6): 1637-45.
115. Li Q, Chen L, Li Q, et al. Cancer increases risk of in-hospital death from COVID-19 in persons <65 years and those not in complete remission. Leukemia **2020**; 34(9): 2384-91.
116. Miyashita H, Mikami T, Chopra N, et al. Do patients with cancer have a poorer prognosis of COVID-19? An experience in New York City. Ann Oncol **2020**; 31(8): 1088-9.

117. Pinto C, Berselli A, Mangone L, et al. SARS-CoV-2 Positive Hospitalized Cancer Patients during the Italian Outbreak: The Cohort Study in Reggio Emilia. Biology (Basel) **2020**; 9(8).
118. Sanchez-Pina JM, Rodríguez Rodriguez M, Castro Quismondo N, et al. Clinical course and risk factors for mortality from COVID-19 in patients with haematological malignancies. Eur J Haematol **2020**.
119. Shah V, Ko Ko T, Zuckerman M, et al. Poor outcome and prolonged persistence of SARS-CoV-2 RNA in COVID-19 patients with haematological malignancies; King's College Hospital experience. Br J Haematol **2020**; 190(5): e279-e82.
120. Stroppa EM, Toscani I, Citterio C, et al. Coronavirus disease-2019 in cancer patients. A report of the first 25 cancer patients in a western country (Italy). Future Oncol **2020**; 16(20): 1425-32.
121. Tian J, Yuan X, Xiao J, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol **2020**; 21(7): 893-903.
122. Yigenoglu TN, Ata N, Altuntas F, et al. The outcome of COVID-19 in patients with hematological malignancy. J Med Virol **2020**.
123. Aries JA, Davies JK, Auer RL, et al. Clinical outcome of coronavirus disease 2019 in haemato-oncology patients. Br J Haematol **2020**; 190(2): e64-e7.
124. Assaad S, Avrillon V, Fournier ML, et al. High mortality rate in cancer patients with symptoms of COVID-19 with or without detectable SARS-COV-2 on RT-PCR. Eur J Cancer **2020**; 135: 251-9.
125. Dufour I, Raedemaeker J, Andreozzi F, et al. COVID-19, impact on myeloma patients. Ann Hematol **2020**; 99(8): 1947-9.
126. Engelhardt M, Shoumariyeh K, Rösner A, et al. Clinical characteristics and outcome of multiple myeloma patients with concomitant COVID-19 at Comprehensive Cancer Centers in Germany. Haematologica **2020**.
127. Garassino MC, Whisenant JG, Huang LC, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. Lancet Oncol **2020**; 21(7): 914-22.
128. Infante MS, González-Gascón YMI, Muñoz-Novas C, et al. COVID-19 in patients with hematological malignancies: A retrospective case series. Int J Lab Hematol **2020**: e13301.
129. Jee J, Foote MB, Lumish M, et al. Chemotherapy and COVID-19 Outcomes in Patients With Cancer. J Clin Oncol **2020**; 38(30): 3538-46.
130. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet **2020**; 395(10241): 1907-18.
131. Lee LY, Cazier JB, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet **2020**; 395(10241): 1919-26.
132. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. Lancet Oncol **2020**; 21(10): 1309-16.

133. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol **2020**; 21(3): 335-7.
134. Mehta V, Goel S, Kabarriti R, et al. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. Cancer Discov **2020**; 10(7): 935-41.
135. Passamonti F, Cattaneo C, Arcaini L, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol **2020**; 7(10): e737-e45.
136. Pinato DJ, Lee AJX, Biello F, et al. Presenting Features and Early Mortality from SARS-CoV-2 Infection in Cancer Patients during the Initial Stage of the COVID-19 Pandemic in Europe. Cancers (Basel) **2020**; 12(7).
137. Pinato DJ, Zambelli A, Aguilar-Company J, et al. Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients. Cancer Discov **2020**.
138. Robilotti EV, Babady NE, Mead PA, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med **2020**; 26(8): 1218-23.
139. Song SH, Chen TL, Deng LP, et al. Clinical characteristics of four cancer patients with SARS-CoV-2 infection in Wuhan, China. Infect Dis Poverty **2020**; 9(1): 82.
140. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Clinical characteristics and outcomes of cancer patients with COVID-19. J Med Virol **2020**.
141. Yarza R, Bover M, Paredes D, et al. SARS-CoV-2 infection in cancer patients undergoing active treatment: analysis of clinical features and predictive factors for severe respiratory failure and death. Eur J Cancer **2020**; 135: 242-50.
142. Zhang H, Wang L, Chen Y, et al. Outcomes of novel coronavirus disease 2019 (COVID-19) infection in 107 patients with cancer from Wuhan, China. Cancer **2020**; 126(17): 4023-31.
143. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol **2020**; 31(7): 894-901.
144. Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. Blood **2020**; 135(21): 1912-5.
145. Thibaud S, Tremblay D, Bhalla S, Zimmerman B, Sigel K, Gabrilove J. Protective role of Bruton tyrosine kinase inhibitors in patients with chronic lymphocytic leukaemia and COVID-19. Br J Haematol **2020**; 190(2): e73-e6.
146. Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). Ann Oncol **2020**; 31(8): 1040-5.
147. Montero F, Martinez-Barrio J, Serrano-Benavente B, et al. Coronavirus disease 2019 (COVID-19) in autoimmune and inflammatory conditions: clinical characteristics of poor outcomes. Rheumatol Int **2020**; 40(10): 1593-8.
148. Pablos JL, Abasolo L, Alvaro-Gracia JM, et al. Prevalence of hospital PCR-confirmed COVID-19 cases in patients with chronic inflammatory and autoimmune rheumatic diseases. Ann Rheum Dis **2020**; 79(9): 1170-3.
149. Santos CS, Morales CM, Alvarez ED, Castro CA, Robles AL, Sandoval TP. Determinants of COVID-19 disease severity in patients with underlying rheumatic disease. Clin Rheumatol **2020**; 39(9): 2789-96.

150. Scire CA, Carrara G, Zanetti A, et al. COVID-19 in rheumatic diseases in Italy: first results from the Italian registry of the Italian Society for Rheumatology (CONTROL-19). Clin Exp Rheumatol **2020**; 38(4): 748-53.
151. Winthrop KL, Brunton AE, Beekmann S, et al. SARS CoV-2 infection among patients using immunomodulatory therapies. Ann Rheum Dis **2020**.
152. Zen M, Fuzzi E, Astorri D, et al. SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: A cross-sectional study on 916 patients. J Autoimmun **2020**; 112: 102502.
153. Zhao J, Pang R, Wu J, et al. Clinical characteristics and outcomes of patients with COVID-19 and rheumatic disease in China 'hot spot' versus in US 'hot spot': similarities and differences. Ann Rheum Dis **2020**.
154. Emmi G, Bettiol A, Mattioli I, et al. SARS-CoV-2 infection among patients with systemic autoimmune diseases. Autoimmun Rev **2020**; 19(7): 102575.
155. Fernandez-Ruiz R, Masson M, Kim MY, et al. Leveraging the United States Epicenter to Provide Insights on COVID-19 in Patients with Systemic Lupus Erythematosus. Arthritis Rheumatol **2020**.
156. Freites Nunez DD, Leon L, Mucientes A, et al. Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis **2020**.
157. Gartshteyn Y, Askanase AD, Schmidt NM, et al. COVID-19 and systemic lupus erythematosus: a case series. Lancet Rheumatol **2020**; 2(8): e452-e4.
158. Kumar U, Goswami RP, Bhadu D, et al. COVID-19 in rheumatic diseases: A random cross-sectional telephonic survey. medRxiv **2020**: 2020.08.09.20170985.
159. Huang Y, Chen Z, Wang Y, et al. Clinical characteristics of 17 patients with COVID-19 and systemic autoimmune diseases: a retrospective study. Ann Rheum Dis **2020**; 79(9): 1163-9.
160. Pablos JL, Galindo M, Carmona L, et al. Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. Ann Rheum Dis **2020**.
161. D'Silva KM, Serling-Boyd N, Wallwork R, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. Ann Rheum Dis **2020**; 79(9): 1156-62.
162. Queiro Silva R, Armesto S, Gonzalez Vela C, Naharro Fernandez C, Gonzalez-Gay MA. COVID-19 patients with psoriasis and psoriatic arthritis on biologic immunosuppressant therapy vs apremilast in North Spain. Dermatol Ther **2020**: e13961.
163. Strippoli D, Barbagallo T, Prestinari F, Russo G, Fantini F. Biologic agents in psoriasis: our experience during coronavirus infection. Int J Dermatol **2020**; 59(8): e266-e7.
164. Fougerousse AC, Perrussel M, Becherel PA, et al. Systemic or biologic treatment in psoriasis patients does not increase the risk of a severe form of COVID-19. J Eur Acad Dermatol Venereol **2020**.
165. Gisondi P, Facheris P, Dapavo P, et al. The impact of the COVID-19 pandemic on patients with chronic plaque psoriasis being treated with biological therapy: the Northern Italy experience. Br J Dermatol **2020**; 183(2): 373-4.

166. Damiani G, Pacifico A, Bragazzi NL, Malagoli P. Biologics increase the risk of SARS-CoV-2 infection and hospitalization, but not ICU admission and death: Real-life data from a large cohort during red-zone declaration. Dermatol Ther **2020**: e13475.
167. Parrotta E, Kister I, Charvet L, et al. COVID-19 outcomes in MS: Observational study of early experience from NYU Multiple Sclerosis Comprehensive Care Center. Neurol Neuroimmunol Neuroinflamm **2020**; 7(5).
168. Fan M, Qiu W, Bu B, et al. Risk of COVID-19 infection in MS and neuromyelitis optica spectrum disorders. Neurol Neuroimmunol Neuroinflamm **2020**; 7(5).
169. Norsa L, Indriolo A, Sansotta N, Cosimo P, Greco S, D'Antiga L. Uneventful Course in Patients With Inflammatory Bowel Disease During the Severe Acute Respiratory Syndrome Coronavirus 2 Outbreak in Northern Italy. Gastroenterology **2020**; 159(1): 371-2.
170. Scaldaferri F, Pugliese D, Privitera G, et al. Impact of COVID-19 pandemic on the daily management of biotechnological therapy in inflammatory bowel disease patients: Reorganisational response in a high-volume Italian inflammatory bowel disease centre. United European Gastroenterol J **2020**; 8(7): 775-81.
171. Allocca M, Fiorino G, Zallot C, et al. Incidence and Patterns of COVID-19 Among Inflammatory Bowel Disease Patients From the Nancy and Milan Cohorts. Clin Gastroenterol Hepatol **2020**; 18(9): 2134-5.
172. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. Gastroenterology **2020**; 159(2): 481-91 e3.
173. Rodriguez-Lago I, Ramirez de la Piscina P, Elorza A, Merino O, Ortiz de Zarate J, Cabriada JL. Characteristics and Prognosis of Patients With Inflammatory Bowel Disease During the SARS-CoV-2 Pandemic in the Basque Country (Spain). Gastroenterology **2020**; 159(2): 781-3.
174. Taxonera C, Sagastagoitia I, Alba C, Manas N, Olivares D, Rey E. 2019 novel coronavirus disease (COVID-19) in patients with inflammatory bowel diseases. Aliment Pharmacol Ther **2020**; 52(2): 276-83.
175. Gubatan J, Levitte S, Balabanis T, Patel A, Sharma A, Habtezion A. SARS-CoV-2 Testing, Prevalence, and Predictors of COVID-19 in Patients with Inflammatory Bowel Disease in Northern California. Gastroenterology **2020**; 159(3): 1141-4 e2.
176. Bezzio C, Saibeni S, Variola A, et al. Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. Gut **2020**; 69(7): 1213-7.
177. Khan N, Patel D, Xie D, Lewis J, Trivedi C, Yang YX. Impact of Anti-Tumor Necrosis Factor and Thiopurine Medications on the Development of COVID-19 in Patients With Inflammatory Bowel Disease: A Nationwide Veterans Administration Cohort Study. Gastroenterology **2020**.
178. Marafini I, Salvatori S, Sena G, Calabrese E, Biancone L, Monteleone G. Low frequency of COVID-19 in inflammatory bowel diseases. Dig Liver Dis **2020**.
179. Lukin DJ, Kumar A, Hajifathalian K, et al. Baseline Disease Activity and Steroid Therapy Stratify Risk of COVID-19 in Patients With Inflammatory Bowel Disease. Gastroenterology **2020**.

180. Maus MV, Lionakis MS. Infections associated with the new 'nibs and mabs' and cellular therapies. Curr Opin Infect Dis **2020**; 33(4): 281-9.
181. Lei S, Jiang F, Su W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine **2020**: 100331.
182. Centers for Disease Control and Prevention. Evaluating and Testing Persons for Coronavirus Disease 2019 (COVID-19). Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html. Accessed 4 May 2020.
183. Khanh N TP, Quach H, et al. . Transmission of SARS-CoV 2 During Long-Haul Flight. . Emerging Infectious Diseases **2020**; 26(11): 2617-24.
184. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature **2020**; 581(7809): 465-9.
185. Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples. The Lancet Infectious diseases **2020**; 20(4): 411-2.
186. Winichakoon P, Chaiwarith R, Liwsrisakun C, et al. Negative Nasopharyngeal and Oropharyngeal Swabs Do Not Rule Out COVID-19. J Clin Microbiol **2020**; 58(5).
187. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet **2020**; 395(10229): 1054-62.