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Diagnostic Testing for Severe Acute Respiratory Syndrome–Related Coronavirus-2

A Narrative Review

Matthew P. Cheng, MDCM; Jesse Papenburg, MD, MSc; Michaël Desjardins, MD; Sanjat Kanjilal, MD, MPH; Caroline Quach, MD, MSc; Michael Libman, MD; Sabine Dittrich, PhD; and Cedric P. Yansouni, MD

Diagnostic testing to identify persons infected with severe acute respiratory syndrome–related coronavirus-2 (SARS–CoV-2) infection is central to control the global pandemic of COVID-19 that began in late 2019. In a few countries, the use of diagnostic testing on a massive scale has been a cornerstone of successful containment strategies. In contrast, the United States, hampered by limited testing capacity, has prioritized testing for specific groups of persons. Real-time reverse transcriptase polymerase chain reaction–based assays performed in a laboratory on respiratory specimens are the reference standard for COVID-19 diagnostics. However, point-of-care technologies and serologic immunoassays are rapidly emerging. Although excellent tools exist for the diagnosis of symptomatic patients in well-equipped laboratories, important gaps remain in screening asymptomatic persons in the incubation phase, as well as in the accurate determination of live viral shedding during convalescence to inform decisions to end isolation. Many affluent countries have encountered challenges in test delivery and specimen collection that have inhibited rapid increases in testing capacity. These challenges may be even greater in low-resource settings. Urgent clinical and public health needs currently drive an unprecedented global effort to increase testing capacity for SARS–CoV-2 infection. Here, the authors review the current array of tests for SARS–CoV-2, highlight gaps in current diagnostic capacity, and propose potential solutions.

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In December 2019, a cluster of patients with pneumonia of unknown cause was reported in Wuhan, China (1). The causative pathogen was subsequently identified as severe acute respiratory syndrome–related coronavirus-2 (SARS–CoV-2) (2), a newly described betacoronavirus. This virus, now recognized as the etiologic agent of COVID-19 disease, is the seventh known coronavirus to infect humans (1). Since the recognition of COVID-19, there has been an exponential rise in the number of cases worldwide. As of 1 April 2020, the World Health Organization reported more than 926 000 cases in more than 195 countries, areas, or territories (3). Reasons for the rapid spread include high transmissibility of the virus (4, 5), especially among asymptomatic or minimally symptomatic carriers (6, 7); the apparent absence of any cross-protective immunity from related viral infections; and delayed public health response measures (8–10).

Age and the presence of comorbid illnesses increase the risk for death among persons with COVID-19 (11, 12). The clinical manifestations of COVID-19 in children are less severe compared with adults, yet age younger than 1 year seems to increase the risk for critical illness (13). Current case-fatality rate estimates range from 0.6% to 7.2% by region and seem to be substantially higher than the 0.1% mortality rate of seasonal influenza (12, 14, 15). However, current estimates of COVID-19 case-fatality rates are probably inflated because of preferential testing in many countries of persons with severe manifestations, who are at risk for death (12, 16). In Germany and South Korea, the case-fatality rates are less than 0.5%, probably because extensive testing revealed a large denominator of mild illness (17).

It has been estimated that before the wide-scale travel restrictions in China, undiagnosed SARS–CoV-2 represented the infection source for 79% of documented cases (7). These observations underscore the critical importance of ample, accurate diagnostic testing in this pandemic. Here, we review the current array of tests for SARS–CoV-2, highlight gaps in current diagnostic capacity, and propose potential solutions.

Methods

We searched the PubMed database for articles on SARS–CoV-2 and diagnostics. The Medical Subject Headings (MeSH) search terms used were "Coronavirus-"[MeSH]; "Coronavirus Infections"[MeSH]; "Severe Acute Respiratory Syndrome"[MeSH]; "Betacoronavirus"[MeSH]; "SARS Virus"[MeSH]; "Polymerase Chain Reaction"[MeSH]; "Reverse Transcriptase Polymerase Chain Reaction"[MeSH]; "High-Throughput Nucleotide Sequencing"[MeSH]; "Sensitivity and Specificity"[MeSH]; "Point-of-Care Testing-"[MeSH]; "Antigens"[MeSH]; "Serology"[MeSH]; "Immunoglobulin G"[MeSH]; "Immunoglobulin M"[MeSH]; "Clustered Regularly Interspaced Short Palindromic Repeats"[MeSH]; "CRISPR-Cas Systems"[MESH]; and "Diagnosis, Differential"[MESH]. Non-MeSH search terms used were *covid*, *SARS*, *SARS-CoV*, *pcr*, *digital droplet PCR*, *next generation sequencing*, *point-of-care test*, *antigen*, *analyte*, *serology*, *Immunoglobulin*, *CRISPR-CAS*, *Diagnos*, and *turn around time*. Only articles including human subjects and those published from 2003 to the present were included. Articles in languages other than English or French were excluded. We screened the results on title and abstract for relevant information. Starting from the articles found in this search, we used a snowball search strategy, scanning useful references and similar articles and retrieving those that were considered relevant. Furthermore, experts were consulted for additional literature. Guidelines and resources from international organizations were used where appropriate. This search was last updated on 1 April 2020.

Key Summary Points

The COVID-19 pandemic demonstrates the essential role of diagnostics in the control of communicable diseases.

Laboratory-based molecular assays for detecting SARS–CoV-2 in respiratory specimens are the current reference standard for COVID-19 diagnosis, but point-of-care technologies and serologic immunoassays are rapidly emerging.

Early, massive deployment of SARS–CoV-2 diagnostics for case finding helped curb the epidemic in several countries.

Urgent clinical and public health needs now drive an unprecedented global effort to increase testing capacity.

The Role of Diagnostic Testing in the SARS–CoV-2 Pandemic

The primary goal of epidemic containment is to reduce disease transmission by reducing the number of susceptible persons in the population or by reducing the basic reproductive number (R0). This number is modulated by such factors as the duration of viral shedding, the infectiousness of the organism, and the contact matrix between infected and susceptible persons (18). Given the lack of effective vaccines or treatments (19), the only currently available lever to reduce SARS–CoV-2 transmission is to identify and isolate persons who are contagious.

Deployment of SARS–CoV-2 testing has varied widely across the globe. A few Asian countries have illustrated the power of preparedness, flexible isolation systems, and intensive case finding. South Korea dramatically slowed the epidemic by implementing an unprecedented testing effort (20). Using innovative measures, South Korea performed more than 300 000 tests (5828.6 tests per million persons) in the 9 weeks after the first case was identified (20, 21). Singapore used a broad case definition, aggressive contact tracing, and isolation (10). Moreover, to identify infected persons not meeting the case definition, Singapore screened patients with pneumonia and influenza-like illnesses in hospitals and primary care settings, severely ill patients in intensive care, and deaths with a possible infectious cause (10). Taiwan and Hong Kong used similar approaches (22). These countries rapidly deployed resource-intensive strategies that prioritized aggressive testing and isolation to interrupt transmission (20, 22).

In the face of widespread transmission, the role of diagnostic testing is contingent on the type of testing available, the resources required for testing, and time to obtain results. For example, rapidly identifying cases among hospitalized patients remains a high priority to properly allocate personal protective equipment and to prevent nosocomial spread with subsequent community transmission (23, 24). Likewise, specific treatment decisions and enrollment in ongoing clinical trials require prompt diagnosis.

Diagnostic Testing: Defining Key Use Cases

Despite the remarkable speed with which accurate diagnostic tests have been developed and made available for SARS–CoV-2 (25), current tools only partially meet several clinically relevant needs. Figure 1 illustrates different indications for diagnostic testing among persons with proven or suspected COVID-19. For each of these, the most important consideration is the clinical decision a test result will help to inform. Test designs must account for several parameters, such as whether the test detects infection directly (such as the virus itself) or indirectly (such as host antibodies), test turnaround time, the ability to perform many tests at the same time (that is, throughput), the need to have a minimum number of specimens before testing (that is, batching), and the ability to perform the test in low-infrastructure settings (such as on cruise ships or in remote communities). The potential for use at the point of care depends on test complexity. The U.S. Food and Drug Administration (FDA) categorizes diagnostic tests by their complexity: Waived tests are available for use at the point of care, whereas moderate- and high-complexity tests must be performed in a laboratory. The intended use also determines which specimen types are ideal or feasible. Finally, it is important to recognize that the acceptable diagnostic accuracy of a test may vary according to use case. For example, sensitivity and specificity requirements of an assay used to confirm results of a screening test need not be as stringent as those of a method used for standalone diagnosis, because the pool of persons being tested is already enriched with true infections. The Foundation for Innovative New Diagnostics has published a detailed assessment of priority use cases to be considered by test developers and policymakers (26).

Who to Test: Current Diagnostic Recommendations in the United States

In response to the rapidly evolving COVID-19 pandemic, countries have used different testing approaches depending on testing capacity, public health resources, and the spread of the virus in the community. In the United States, diagnostic testing indications and capacity were limited at the beginning of the outbreak, largely because of regulatory hurdles for the use of new tests. To expand access to testing, the FDA released policies to allow laboratories to use their validated assays in a more timely manner (27). On 4 March, the Centers for Disease Control and Prevention (CDC) removed restrictive testing criteria, recommending that clinicians use their judgment to determine whether a test should be performed (28). Because testing capacity remains suboptimal (27), the implementation of this recommendation remains a challenge. The CDC still recommends priority for testing 3 groups: hospitalized

patients with presentations compatible with COVID-19, other symptomatic persons at risk for poor outcomes, and persons who had close contact with someone with suspected or confirmed COVID-19 within 14 days of illness onset or have a history of travel in an affected area (28). These patients should be evaluated with a molecular diagnostic test, as described later. The CDC does not recommend testing asymptomatic persons.

How to Test: Diagnostic Tests in Use or Under Evaluation

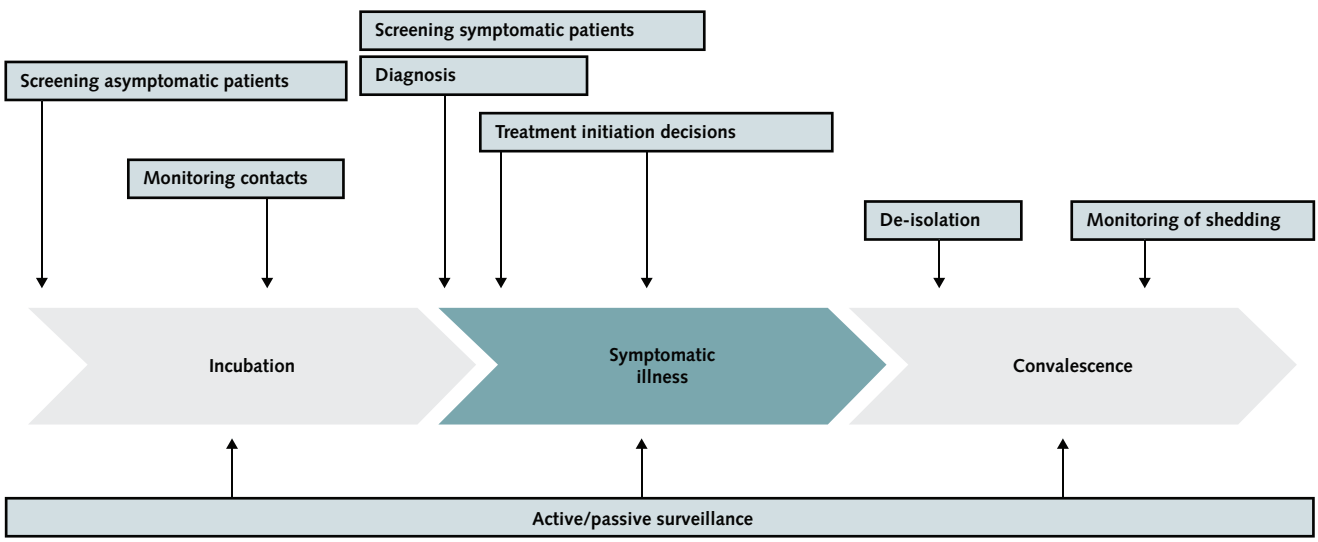
Although real-time reverse transcriptase polymerase chain reaction (RT-PCR)–based assays performed in the laboratory on respiratory specimens are the cornerstone of COVID-19 diagnostic testing, several novel or complementary diagnostic methods are being developed and evaluated (16). Figure 2 depicts the adequacy of the principal assay types used or proposed for COVID-19 for 4 key use cases. Among patients diagnosed with COVID-19, the occurrence of concomitant viral infections has been reported to range from below 6% (29) to greater than 60% (30). As a result, it is not possible to rule out SARS–CoV-2 infection merely by detecting another respiratory pathogen.

Laboratory-Based Molecular Testing

The current diagnostic strategy recommended by the CDC to identify patients with COVID-19 is to test samples taken from the respiratory tract to assess for the presence of 1 or several nucleic acid targets specific to SARS–CoV-2 (25). A nasopharyngeal specimen is the preferred choice for swab-based SARS–CoV-2 testing, but oropharyngeal, mid-turbinate, or anterior nares samples also are acceptable (31, 32). Samples should be obtained by using a flocked swab, if available, to enhance the collection and release of cellular material. Swabs with an aluminum or plastic shaft are preferred. Swabs that contain calcium alginate, wood, or cotton should be avoided, because they may contain substances that inhibit PCR testing. Ideally, swabs should be transferred into universal transport medium immediately after sample collection to preserve viral nucleic acid. Samples taken from sputum, endotracheal aspirates, and bronchoalveolar lavage also may be sent directly to the microbiology laboratory for processing, and may have greater sensitivity than upper respiratory tract specimens (33). Inadequate sample collection may result in a false-negative test. After specimen collection, samples undergo RNA extraction followed by qualitative RT-PCR for target detection.

In the United States, the CDC has developed the most widely used SARS–CoV-2 assay. The kit contains PCR primer–probe sets for 2 regions of the viral nucleocapsid gene (N1 and N2), and for the human RNase *P* gene to ensure the RNA extraction was successful. This assay differs from the World Health Organization primer–probe sets, which target the SARS–CoV-2 RNA-dependent RNA polymerase (*RdRP*) and envelope (*E*) genes (25). Both assays have high analytic sensitivity and specificity for SARS–CoV-2, with minimal cross-reactivity with other circulating strains of coronaviruses, and both use a cycle threshold of less than 40 as the criterion for positivity. The CDC kit may be used by state public health laboratories, other laboratories determined by the state to be qualified, and clinical laboratories that meet the regulatory requirements of the

Figure 1. Examples of use cases for diagnostic testing among persons with proven or suspected COVID-19.



A test well suited for one use case (such as epidemiologic surveillance) may be completely inadequate for another (such as rapid screening of symptomatic patients for allocation of personal protective equipment). For test results to enable a specific clinical decision, test developers, policymakers, and clinicians need to consider each of these with respect to the intention of testing and the population being tested as specifically as possible. For the moment, most use cases placed above the green and gray bar are best met by nucleic acid amplification tests, whereas detection of host-derived antibodies directed against SARS–CoV-2 will be crucial for surveillance, epidemic forecasting, and determination of SARS–CoV-2 immunity. SARS–CoV-2 = severe acute respiratory syndrome–related coronavirus-2.

Figure 2. Heat map showing the adequacy of principal assay types (rows) for 4 key use cases.

Assay Type	Selected Use Case: Screening during incubation/asymptomatic phase	Diagnosis of symptomatic disease	Screening for viral shedding in convalescence phase for de-isolation decisions	Epidemiologic surveillance
Laboratory-based RT-PCR or NAAT assay	Unknown/insufficient negative predictive value	Current reference standard	Unknown/insufficient negative predictive value	Passive surveillance Unknown/insufficient negative predictive value for case finding
POC sample-to-answer NAAT assay	Unknown/insufficient negative predictive value	Likely comparable to reference standard	Unknown/insufficient negative predictive value	Passive surveillance Unknown/insufficient negative predictive value for case finding
Antigen detection POC*	Unknown/insufficient negative predictive value	Yet to be developed	Likely insufficient negative predictive value	Likely lower sensitivity than NAAT will hamper predictive value with low prevalence
Serology IgM/IgG detection (POC or laboratory based)*	Likely false-negative in early disease	Likely false-negative in early disease†	Typically do not mirror disease activity	Serosurveys could assess individual and population immunity*

Medium green cells are those for which currently available tools are well adapted for most intended uses within the use case in terms of diagnostic accuracy, format, and turnaround time. Light green cells are those for which assays that are available or projected in the short term are useful but have important limitations for their use (for example, current RT-PCR assays may yield false-negative results for persons in the incubation phase with a low viral load). Dark green cells are those for which the assay type does not meet the needs of the use case. NAAT, nucleic acid amplification test; POC = point of care; RT-PCR = reverse transcriptase polymerase chain reaction.

* This assumes that assays in development or currently undergoing regulatory evaluation prove to be accurate.

† The utility of antibody detection assays for diagnosing acute infections is probably very limited around the time of symptom onset, when viral shedding and transmission risk seem to be highest. Thus, although such tests may have a role among persons presenting late in the course of their infection, the potential for misuse is high.

Clinical Laboratories Improvement Amendment (CLIA) to perform high-complexity testing (27). Dozens of laboratories have applied for Emergency Use Authorization (EUA) from the FDA for their own laboratory-developed assays (34). The FDA also has granted an EUA for several commercial assays (35), further expanding the ability of clinical laboratories to use these platforms (Table).

The lack of an established reference standard, use of differing sample collection and preparation methods, and an incomplete understanding of viral dynamics across the time course of infection hamper rigorous assessment of the diagnostic accuracy of the many newly introduced SARS–CoV-2 assays (36). Serum and urine are usually negative for the presence of viral nucleic acid, regardless of illness severity (33). Of importance, the ability of RT-PCR assays to rule out COVID-19 on the basis of upper respiratory tract samples obtained at a single time point remains unclear. Conversely, after a patient has had a positive test result, several authorities have recommended obtaining at least 2 negative upper respiratory tract samples, collected at intervals of 24 hours or longer, to document SARS–CoV-2 clearance (37, 38).

Point-of-Care Molecular Diagnostics

Low-complexity, rapid (results within 1 hour) molecular diagnostic tests for respiratory viral infections that are CLIA waived (FDA approved for use outside the laboratory by nonlaboratory personnel) include cartridge-based assays on platforms that include the Abbott ID NOW (Abbott Laboratories), BioFire FilmArray (bioMérieux), cobas Liat (Roche Diagnostics), and GeneXpert (Cepheid) (39).

Rapid point-of-care assays for SARS–CoV-2 on instruments such as these will be critical to expand point-of-care testing. The Xpert Xpress SARS–CoV-2 test (Cepheid) has received an FDA EUA and is performed on the GeneXpert platform, which is already widely used for tuberculosis and HIV testing, especially in low- and middle-income countries. This capacity might be useful to scale up testing across the world as well as in settings where rapid results at the point of care would

enable clinical decisions, although testing throughput may be a limiting factor.

Antigen Detection Tests

Tests that detect respiratory syncytial virus or influenza virus antigens by immunoassay directly from clinical specimens have been commercially available for decades, are of low complexity, and may provide results within minutes at the point of care (40). Current tools for influenza and respiratory syncytial virus suffer from suboptimal sensitivity to rule out disease (41, 42); the same challenge would probably exist for SARS–CoV-2, and tests would need to be implemented with clear guidance on correct interpretation. Prototypes of such tests for other novel coronaviruses have not received regulatory approval (43, 44) but are under development (45). Monoclonal antibodies against the nucleocapsid protein of SARS–CoV-2 have been generated, which might form the basis of a future rapid antigen detection test (20).

Serology

Serologic tests that identify antibodies (such as IgA, IgM, and IgG) to SARS–CoV-2 from clinical specimens (such as blood or saliva), such as enzyme-linked immunosorbent assays, may be less complex than molecular tests and have the potential to be used for diagnosis in certain situations (46). However, their utility for diagnosing acute infections is probably limited around the time of symptom onset, when viral shedding and transmission risk seem to be highest (32). Antibody responses to infection take days to weeks to be reliably

Table. The 28 Commercial SARS–CoV-2 in Vitro Diagnostic Assays Given an EUA From the FDA as of 4 April 2020

Date in 2020 That EUA Was Issued*	Manufacturer	Test Name	Test Type
Currently FDA authorized for use in clinical laboratories			
3 April	Luminex Corporation	ARIES SARS-CoV-2 Assay	NAAT
3 April	Co-Diagnostics	Logix Smart Coronavirus Disease 2019 (COVID-19) kit	NAAT
3 April	ScienCell Research Laboratories	SARS–CoV-2 Coronavirus Real-time RT-PCR (RT-qPCR) Detection Kit	NAAT
2 April	Becton, Dickinson and Company (BD)	BioGX SARS–CoV-2 Reagents for BD MAX System	NAAT
1 April	Ipsum Diagnostics	COV-19 IDx assay	NAAT
1 April	Cellex	qSARS–CoV-2 IgG/IgM Rapid Test	Lateral flow chromatographic immunoassay
30 March	NeuMoDx Molecular	NeuMoDx SARS–CoV-2 Assay	NAAT
30 March	QIAGEN GmbH	QIAstat-Dx Respiratory SARS–CoV-2 Panel	NAAT
27 March	Luminex Molecular Diagnostics	NxTAG CoV Extended Panel Assay	NAAT
26 March	BGI Genomics	Real-Time Fluorescent RT-PCR Kit for Detecting SARS-2019-nCoV	NAAT
25 March	Avellino Lab USA	AvellinoCoV2 test	NAAT
24 March	PerkinElmer	PerkinElmer New Coronavirus Nucleic Acid Detection Kit	NAAT
23 March	BioFire Defense	BioFire COVID-19 test†	NAAT
20 March	Primerdesign	COVID-19 genesig Real-Time PCR assay	NAAT
19 March	GenMark Diagnostics	ePlex SARS–CoV-2 Test	NAAT
19 March	DiaSorin Molecular	Simplexa COVID-19 Direct assay†	NAAT
18 March	Abbott Molecular	Abbott RealTime SARS–CoV-2 assay	NAAT
17 March	Quest Diagnostics Infectious Disease	Quest SARS–CoV-2 rRT-PCR	NAAT
17 March	Quidel Corporation	Lyra SARS–CoV-2 Assay	NAAT
16 March	LabCorp	COVID-19 RT-PCR test	NAAT
16 March	Hologic	Panther Fusion SARS–CoV-2 Assay	NAAT
13 March	Thermo Fisher Scientific	TaqPath COVID-19 Combo Kit	NAAT
12 March	Roche Molecular Systems	cobas SARS–CoV-2 Test	NAAT
29 February	Wadsworth Center, New York State Department of Public Health (CDC)	New York SARS–CoV-2 Real-time Reverse Transcriptase (RT)-PCR Diagnostic Panel	NAAT
4 February	CDC	2019-nCoV Real-Time RT-PCR Diagnostic Panel	NAAT
Currently FDA authorized for use outside the clinical laboratory environment			
27 March	Abbott Diagnostics Scarborough	ID NOW COVID-19 assay	NAAT
23 March	Mesa Biotech	Accula SARS–CoV-2 Test	NAAT
20 March	Cepheid	Xpert Xpress SARS–CoV-2 test	NAAT

CDC = Centers for Disease Control and Prevention; EUA = Emergency Use Authorization; FDA = U.S. Food and Drug Administration; NAAT = nucleic acid simplification test; SARS–CoV-2 = severe acute respiratory syndrome–related coronavirus-2.
* Dates of EUA are indicated to highlight the speed with which the diagnostic landscape is changing.
† Performed on instruments for which other assays from the same manufacturer have been FDA authorized for use outside the clinical laboratory environment, indicating the potential for a similar designation for SARS–CoV-2 assays in the future.

detectable (46). Negative results would not exclude SARS–CoV-2 infection, particularly among those with recent exposure to the virus. Cross-reactivity of antibody to non–SARS–CoV-2 coronavirus proteins is also a potential problem, whereby positive results may be the result of past or present infection with other human coronaviruses (47). Serologic assays might be more relevant in scenarios in which patients present to medical care with late complications of disease, when RT-PCR may be falsely negative, because viral shedding drops over time (48).

The development of serologic assays that accurately assess prior infection and immunity to SARS–CoV-2 will be essential for epidemiologic studies, ongoing surveillance, vaccine studies, and potentially for risk assessment of health care workers. Immunoassays are already on the market in some countries, but their diagnostic accuracy and optimal use remain undefined.

Ancillary Diagnostic Tests

The optimal use of diagnostic imaging, biomarkers, and other nonmicrobiologic tests is rapidly evolving.

Radiographic Tests

Many centers have evaluated the utility of chest imaging for diagnosis. On chest radiography, bilateral pneumonia is the most frequently reported feature (range, 11.8% to 100%) and is more common than a unilateral focus (49, 50). Computed tomography is regarded as more sensitive than radiography, with several cohort studies reporting that most patients (77.8% to 100%) had ground glass opacities. Other features commonly reported with COVID-19 on chest computed tomography include a peripheral distribution, fine reticular opacities, and vascular thickening (51). Compared with serial nasopharyngeal sampling, chest computed tomography may be more sensitive than an RT-PCR test at a single time point for the diagnosis of COVID-19 (52, 53). In addition, artificial intelligence may help distinguish COVID-19 from other etiologic agents of community-acquired pneumonia (54). However, these findings are not completely specific to COVID-19 and do not exclude a co-infection or an alternative diagnosis (55).

Biomarkers Associated With COVID-19 Patients

The most common laboratory features reported in patients with COVID-19 include decreased albumin (75.8% [95% CI, 30.5% to 100%]), elevated C-reactive protein (58.3% [CI, 21.8% to 94.7%]), and elevated lactate dehydrogenase levels (57.0% [CI, 38.0% to 76.0%]), and lymphopenia (43.1% [CI, 18.9% to 67.3%]) (56). Other biomarkers that have been reported include increased erythrocyte sedimentation rates; elevated aspartate aminotransferase, alanine aminotransferase, and creatinine kinase levels; leukopenia; leukocytosis; and increased bilirubin and creatinine levels (57–59). Such findings are not surprising, because these biomarkers represent an inflammatory host response to SARS–CoV-2 or are early markers of end-organ dysfunction, similar to that seen in patients with sepsis (60). No biomarker or combination of biomarkers currently exists that is sensitive or specific enough to establish a diagnosis of COVID-19, or to pragmatically predict its clinical course.

Unmet Needs and the Diagnostic Test Pipeline

Scaling Up Access to Diagnostic Testing

In the face of a public health emergency, important first steps to expand testing capacity include relaxing and streamlining regulatory requirements and procedures. Local public health laboratories and academic diagnostic laboratories in the United States are being rapidly enabled to perform EUA-granted commercial assays and laboratory-developed tests using research use–only reagents (61). University research laboratories could also add capacity, although concerns exist regarding quality control and the absence of protocols for managing clinical specimens. Flexibility regarding nucleic acid extraction methods and amplification instruments when using CDC protocols is being introduced (34). National agencies are expeditiously making materials for test development and validation available to clinical laboratories and diagnostic test manufacturers.

Safely evaluating clinically stable persons for COVID-19 at traditional health care access points is resource intensive and slow, and risks exposing staff to infection. Many jurisdictions are enabling innovative testing venues, such as external tents or drive-through or "phone booth" testing, as well as home assessment teams to expedite specimen collection while limiting potential exposures (62). Telemedicine combined with at-home nasal swab self-testing also has been proposed (63). Of importance, in jurisdictions without universal health care coverage, policy solutions must be introduced to eliminate financial barriers to testing for uninsured and underinsured patients. Efforts to increase accessibility of testing for multiple use cases need to be coupled to appropriate public health interventions to isolate infected persons and their contacts.

Alternatives to Usual Specimen Types, Collection Devices, and Transport Media

Nasopharyngeal swabs are the recommended specimen for molecular analysis. The sudden demand for flocked nasopharyngeal swabs and viral transport medium generated by the pandemic has put enormous pressures on supply chain capacities for these products. As of 19 March 2020 the CDC made oropharyngeal, mid-turbinate, and nasal swabs acceptable specimen types if nasopharyngeal swabs are not available (31). Early-morning posterior oropharyngeal saliva samples (coughed up by clearing the throat) also have been assessed as useful specimen types and would not require use of a swab (48). The CDC has released a standard operating procedure for laboratories to create their own viral transport medium (64); other solutions also may be used if viral transport medium is unavailable, including phosphate-buffered saline, liquid Amies, and normal saline (65). The FDA has provided

guidance on its Web site for alternative materials to collect and transport samples for RT-PCR SARS–CoV-2 assays (34). The diagnostic value of molecular testing of nonrespiratory specimens currently is unclear.

Diagnostics Pipeline in the Short and Medium Term

Although excellent tools exist for the diagnosis of symptomatic patients in well-equipped laboratories, important gaps remain in screening asymptomatic persons in the incubation phase, as well as for the accurate determination of live viral shedding among patients in the convalescence phase to inform de-isolation decisions (Figure 2). Further, it is critical to advance solutions that require less well-equipped laboratories to curb the pandemic globally. The Foundation for Innovative New Diagnostics (FIND) and others have created online resources to collate the rapidly evolving set of assays at various stages of development, from proof of concept to full regulatory approval (20, 53). Simple antigen-based tests, if sensitive enough, might be useful in lower-resource and home settings to inform quarantine and spatial distancing measures for patients without severe illness and their contacts. Novel technologies, such as Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR)-based diagnostics are being used to develop rapid, simple, low-cost, portable, temperature-stable assays for deployment in the field in nontraditional and resource-limited settings, such as airports and border crossings (20, 51, 54). Other technologies might be deployed to lower-resource settings if they can be standardized. For example, it might be possible to leverage existing loop-mediated isothermal amplification testing networks established for other diseases, such as human African trypanosomiasis surveillance (66).

Other Considerations

Critical considerations for diagnostics used for epidemic diseases of public health importance include the quality assurance and regulatory frameworks surrounding testing. Mature regulatory agencies have developed mechanisms to account for emergencies, such as the FDA's EUA stream, but pragmatic solutions must be found to facilitate wide-scale, independent evaluation of emerging tests.

Initially, the need for elaborate biosafety precautions and inconsistent recommendations for their application across regions severely hampered COVID-19 testing. Although these continue to evolve, current recommendations in Canada and the United States acknowledge that nonpropagative work for molecular testing may be performed in containment level 2 conditions found in routine diagnostic laboratories and provide specific guidance on diagnostic testing of specimens conducted outside a biosafety level 2 laboratory, such as rapid respiratory testing performed at the point of care (67) .

Conclusion

The COVID-19 pandemic has dramatically highlighted the essential role of diagnostics in the control of communicable diseases. Intensive diagnostics deployment probably contributed to the success of a few countries in controlling transmission. Urgent clinical and public health needs now drive an unprecedented global effort to increase SARS–CoV-2 testing capacity. Finally, the blinding speed with which COVID-19 has spread illustrates the need for preparedness and long-term investments in diagnostic testing.

From McGill University Health Centre and McGill Interdisciplinary Initiative in Infection and Immunity, Montreal, Quebec, Canada (M.P.C.); McGill Interdisciplinary Initiative in Infection and Immunity and Montreal Children's Hospital, Montreal, Quebec, Canada (J.P.); Brigham and Women's Hospital, Boston, Massachusetts, and Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada (M.D.); Brigham and Women's Hospital, Harvard Medical School, and Harvard Pilgrim Health Care Institute, Boston, Massachusetts (S.K.); CHU Sainte-Justine, Université de Montréal, Montreal, Quebec, Canada (C.Q.); McGill University Health Centre, McGill Interdisciplinary Initiative in Infection and Immunity, and McGill University, Montreal, Quebec, Canada (M.L., C.P.Y.); and Foundation of Innovative New Diagnostics, Malaria and Fever Program, Geneva, Switzerland, and University of Oxford, Oxford, United Kingdom (S.D.).

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Corresponding Author: Matthew P. Cheng, MDCM, Division of Infectious Diseases, McGill University Health Centre, 1001 Decarie Boulevard, E05.1709, Montreal, Quebec, Canada H4A 3J1; e-mail, matthew.cheng@mcgill.ca.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Dr. Cheng, MDCM, Division of Infectious Diseases, McGill University Health Centre, 1001 Decarie Boulevard, E05.1709, Montreal, Quebec, Canada H4A 3J1.
Dr. Papenburg: Division of Infectious Diseases, Montreal Children's Hospital, 1001 Decarie Boulevard, E05.1905, Montreal, Quebec, Canada H4A 3J1.
Dr. Desjardins: Division of Transplant Infectious Disease, Brigham and Women's Hospital, 75 Francis Street, PBB-A4, Boston, MA 02115.
Dr. Kanjilal: Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401, East Boston, MA 02115.
Dr. Quach: Divison of Infectious Diseases, CHU Sainte-Justine, 3175, ch. Côte Ste-Catherine, B.17.102, Montreal, Quebec, Canada H3T 1C5.
Dr. Libman: Division of Infectious Diseases, McGill University Health Centre, 1001 Decarie Boulevard, E05.1830, Montreal, Quebec, Canada H4A 3J1.
Dr. Dittrich: Foundation of Innovative New Diagnostics (FIND), Campus Biotech, Chemin des Mines 91 202, Geneva, Switzerland.
Dr. Yansouni: Division of Infectious Diseases, McGill University Health Centre, 1001 Decarie Boulevard, EM3.3242, Montreal, Quebec, Canada H4A 3J1.

Author Contributions: Conception and design: M.P. Cheng, J. Papenburg, M. Desjardins, M. Libman, S. Dittrich, C.P. Yansouni.
Analysis and interpretation of the data: M.P. Cheng, J. Papenburg, S. Dittrich, C.P. Yansouni.
Drafting of the article: M.P. Cheng, J. Papenburg, M. Desjardins, S. Kanjilal, M. Libman, S. Dittrich, C.P. Yansouni.
Critical revision for important intellectual content: M.P. Cheng, J. Papenburg, M. Desjardins, S. Kanjilal, C. Quach, M. Libman, C.P. Yansouni.
Final approval of the article: M.P. Cheng, J. Papenburg, M. Desjardins, S. Kanjilal, C. Quach, M. Libman, S. Dittrich, C.P. Yansouni.
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Collection and assembly of data: M.P. Cheng, J. Papenburg, C.P. Yansouni.