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REVIEW

Point-of-care COVID-19 testing in the emergency department: current status and future prospects

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ABSTRACT

Introduction: This expert review outlines current and future point-of-care technologies for the diagnosis of the SARS-CoV-2 virus, which is responsible for causing coronavirus disease COVID-19 in the emergency department. COVID-19 first emerged in late 2019 and is responsible for a range of presentations from minor upper respiratory tract symptoms to severe pneumonia and multisystem organ failure. Among the technologies available include the gold standard of molecular point-of-care tests as well as antigen detection tests.

Areas covered: We discuss point-of-care molecular tests including multiplex, targeted, and single plex panels as well as various antigen testing methodologies in terms of availability and performance characteristics. In addition, we focus on current testing best practices and considerations for point-of-care testing in the emergency department based on a search of the literature available in PubMed to date and a review of FDA and CDC guidance.

Expert opinion: While there have been many advances in SARS-CoV-2 point-of-care testing, there remain challenges to implementation in the emergency department setting. A paradigm shift is needed to improve diagnosis and clinical outcomes.

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1. Introduction

Coronavirus disease (COVID-19), which is caused by the SARS-CoV-2 coronavirus, first emerged in Wuhan, China, in late 2019 and was first described as a series of atypical pneumonia cases [1]. COVID-19 causes a wide range of manifestations, including fever, cough, upper respiratory, and gastrointestinal symptoms [2]. The virus can be transmitted asymptomatically or pre-symptomatically [3,4]. Disease severity is greater in the elderly and those with comorbidities, including cardiovascular disease and diabetes [4]. Non-White and populations of lower socio-economic status who have more interaction with the public and are more likely to live in crowded conditions have been more severely impacted [5,6]. As of February 11, 2021, the virus has caused nearly 108 million cases and over 2 million deaths worldwide in a global pandemic [7]. In the US, an initial lack of availability of rapid and accurate testing led to difficulties in the identification of cases and contact tracing, and we are currently in the mitigation phase. As of February 11, 2021, the number of cases in the US is over 27 million and reported deaths at 474,000 [7]. The number of cases is estimated to be possibly over ten times greater than the cases reported [8].

2. Molecular point-of-care tests for COVID-19

The SARS-CoV-2 pandemic has expanded the rise of point-of-care (POC) testing in the emergency department (ED) to improve patient flows and provide results in a timely manner. Point-of-care testing is defined as medical testing at or near the site of patient care and improving outcomes by accelerating the time from test administration to treatment (i.e. therapeutic turnaround time). Point-of-care testing is performed by clinical staff in the ED and result in under 1 hour, whereas near POC tests are performed in the laboratory by trained laboratory personnel and result in under 2 hours. Principles of development of new POC devices have been driven through the World Health Organization guidelines, known as the ASSURED guidelines. The guidelines call for affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and test results that are delivered to the end-users [9].

As it applies to COVID-19 testing, POC tests for the ED can come in multiple formats including large syndromic panels, targeted panels which commonly include primers for influenza, SARS-CoV-2, and respiratory syncytial virus, and tests that only detect the SARS-CoV-2 virus.

2.1. Multiplex respiratory panels

Several multiplex respiratory panels that simultaneously detect greater than five pathogens have been Food and Drug Administration (FDA) emergency use authorized (EUA) and contain targets for the SARS-CoV-2 virus. These panels vary in the number of targets included, performance characteristics, turnaround times, and levels of complexity. The use

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Article Highlights

- We review molecular and antigen tests available for the detection of SARS-CoV-2 at the point of care.
- Antigen tests in general have poorer performance in asymptomatic patients.
- Testing for SARS-CoV-2 at the point of care may have an important role in antimicrobial stewardship strategies and infection prevention.
- Workflow considerations are important when implementing new diagnostic tests for SARS-CoV-2 in the emergency department.
- Gaps in testing remain namely in the paucity of research on the impact of these tests on clinical management and outcomes for patients being evaluated for COVID-19.

of multiplex panels to simultaneously detect and identify respiratory pathogens may simplify testing algorithms and improve the sensitivity and speed of diagnosis compared to those of conventional methods such as low-plex PCR testing, antigen testing or viral culture. Currently, there are four multiplex panels that have received EUA for the detection of respiratory pathogens, including SARS-CoV-2: (i) NxTAG Respiratory Pathogen Panel (Luminex, Austin, TX), (ii) the FilmArray respiratory panel 2 (bioMerieux, Marcy L'Etoile, FR), (iii) ePlex RP (GenMark Dx, Carlsbad, Ca), and (iv) the QIAstat-DX Respiratory SARS-CoV-2 Panel (Qiagen, Germantown, MD) [10].

Each of the respiratory pathogen panels is FDA authorized for use in locations that are licensed to perform moderate or high complexity testing per Clinical and Laboratory Improvement Amendments (CLIA) standards, although the FilmArray is also authorized in a CLIA-waived format known as the RP2.1-EZ. To remain CLIA-waived the FilmArray RP2.1-EZ must be run on the accompanying CLIA-waived FilmArray 2.0 EZ analyzer. Each of the multiplex respiratory pathogen panels is FDA authorized for use with nasopharyngeal swabs [10]. The comprehensive sensitivity and specificity of the multiplex panels were reviewed by Ramanan et al. and found sensitivities ranging from 84% to 98% and specificities ranging from 99% to 100% for all targets [11].

In hospitalized patients with COVID-19, the routine use of molecular POCT in ED admissions was evaluated in a study published in The Lancet Respiratory Medicine [12]. In this study, Brendish et al. enrolled 1054 patients in a non-randomized, prospective, interventional study evaluating the impact of a multiplex panel performed in the POC compared to patients where specimens were sent to an on-site central laboratory for testing. From the study population, 197 patients tested positive for the SARS-CoV-2 virus with a median time to result in the POC arm of 1.7 hours compared to 21.3 hours in the laboratory testing arm. While not measured, the reduction in time to results potentially allowed for improvements in infection control measures, patient flow, and recruitment into clinical trials compared with the use of laboratory-based polymerase chain reaction (PCR) testing [12].

2.2. Targeted panels

Targeted panels for the detection of respiratory viruses detect five or fewer viruses using amplification of the viral nucleic acid. Similar to other molecular approaches, the panels can use polymerase chain reaction, helicase-dependent amplification, or other methods for nucleic acid amplification. Currently, there are numerous commercially available, multianalyte targeted panels that have received FDA authorization for the detection of influenza A and B, Respiratory Syncytial Virus (RSV), and SARS-CoV-2; however, the majority of the FDA authorized tests are only cleared for use in high or moderately complex laboratories. For use in the ED, only two respiratory pathogen targeted panels exhibit workflows that would be suitable for use in a near-patient environment, devoid of laboratory professionals. These assays include the Roche cobas SARS-CoV-2 and Influenza A/B Nucleic Acid Test for use on the cobas LIAT (Roche, Indianapolis, IN) and the Cepheid GeneXpert Xpress SARS-CoV-2/Flu/RSV assay (Cepheid, Sunnyvale, CA). The LIAT assay is FDA authorized for use in laboratories with a CLIA moderate or high complexity certification or in the POC for locations operating under a CLIA Waiver certificate. The LIAT is authorized for use with healthcare provider collected nasal and nasopharyngeal (NP) specimens and healthcare provider supervised, self-collected nasal swabs [13]. Results on the LIAT are available within 20 minutes of placing the specimen on the instrument [14]. Performance of the LIAT was evaluated by Hansen et al. using NP swabs collected from 444 patients between Sept and Oct 2020 [15]. The authors found high positive (100% PPA) and negative (97.4% NPA) agreement with the laboratory-based cobas 6800/8800 (Roche Diagnostics, Indianapolis, IN) which results in several hours.

Similarly, the Xpert Xpress SARS-CoV-2/Flu/RSV assay is also FDA authorized for use in laboratories with a CLIA moderate or high complexity certification or in the POC for locations operating under a CLIA Waiver. The Xpert assay is available in a single or multiplex panel and is authorized for use with NP swab, nasal swab, or nasal wash/ aspirate specimens collected from individuals suspected of respiratory viral infection consistent with COVID-19 by their healthcare provider [16]. For testing that is performed in the POC under a CLIA Waiver, only NP or nasal swabs collected by a healthcare provider are authorized [17]. Loeffelholz et al. evaluated the Xpert assay in a multi-site clinical trial enrolling 483 upper respiratory specimens and comparing the performance of the Xpert with laboratory standard of care nucleic acid amplification testing (NAAT). When compared to one of three laboratory-based PCR tests the Xpert assay demonstrated 99.5% positive agreement and 95.8% negative agreement with the standard of care Nucleic Acid Amplification Testing (NAAT) [18]. Additional studies by Mostafa et al. and others have demonstrated similar findings [19–21], with results available in 50 minutes.

When compared with other POC methods, the Xpert Xpress assay has demonstrated impressive performance. In a study evaluating the LOD of sample-to-answer platforms, Zhen et al.

determined the Xpert and ePlex systems to have an LOD of 1000 copies/mL which was considerably lower than the LOD of ID NOW (to be discussed in the next section) which had a limit of detection (LOD) of 20,000 copies/mL [22]. Xpert Xpress also had the highest positive percent agreement (PPA) compared to a laboratory-based reference standard (98.3%), followed by ePlex (91.4%) and ID NOW (87.7%). All three assays showed 100% negative percent agreement (NPA) [22].

2.3. SARS-CoV-2 single-plex molecular tests

As of the date of publication of this review, more than 200 molecular tests for the detection of SARS-CoV-2 have been authorized by the FDA for Emergency Use [23]. The majority of tests are intended for use in the clinical laboratory and are cleared for use in laboratories with a moderate or high complexity CLIA certificated and thus are outside the scope of this review focused on the ED setting. To narrow the scope of tests for this review, we will only overview tests that are FDA approved for use in the POC with a CLIA Waiver and have an intended use of detection of the virus (serological tests are excluded). Currently, molecular tests that are FDA authorized for detection of the SARS-CoV-2 virus in the POC include (Table 1A): (i) Visby Medical COVID-19 POC Test (Visby Medical, San Jose, CA), (ii) Accula SARS-CoV-2 Test (Mesa BioTech, San Diego, CA), (iii) ID NOW COVID-19 (Abbott Diagnostics, Scarborough, ME), (iv) Cue COVID-19 test (Cue Health, San Diego, CA), and the (v) Lucira COVID-19 All-in-One (Lucira, Emeryville, CA) [23].

While there is a paucity of peer-reviewed studies evaluating the analytical performance, clinical performance, or outcome benefits of many of the POC molecular SARS-CoV-2 tests, two systems, the Accula and ID NOW tests have published studies. Hogan et al. compared performance of the Accula assay to the Stanford Health EUA LDT using 100 pediatric and adult NP specimens. The authors found 84% positive agreement and 100% negative agreement among the tests. Discrepancies between the Accula and the reference method were typically around in specimens with a median cycle threshold of 37.7, indicating false-negative results from the Accula assay in patients with a low viral burden [24].

Among the best evaluated of the POC molecular COVID-19 tests is the Abbott ID NOW. Performance of the test is greatly dependent upon the type of specimen collected and the use of viral transport media (transport media has been reported to result in dilution of the specimen causing decreased sensitivity in low positive specimens [25]. Most studies report PPA of 53–94% [26–31], with the majority of studies reporting PPA around 75. However, in one study by Basu et al. compared the performance of the ID Now to the Xpert Xpress assay when NP specimens were collected from symptomatic patients on dry swabs in the ED. From dry swabs, the ID Now exhibited a PPA of 54.8% (17 of 31 specimens) and an NPA of 98.6% (69 of 70 specimens) [32].

3. SARS-CoV-2 antigen testing

Immunoassays are used to detect SARS-CoV-2 viral antigens such as the spike and nucleocapsid proteins. Antigen testing offers a compromise between clinical performance (e.g. sensitivity and specificity) versus speed and accessibility. Unlike molecular approaches, immunoassay reagent production is less constrained and testing platforms can range from point-of-care formats to full-sized automated analyzers that are commonly available in hospital laboratories. Antigen testing may be limited to testing in symptomatic individuals only, but more recently, some tests have received FDA authorization for testing in asymptomatic populations. Negative antigen results in symptomatic patients may require follow-up testing via molecular approaches. Results may be qualitatively or quantitatively reported.

3.1. Antigen testing methods

Immunoassays rely on the unique nature of antibodies to bind to specific antigens. Briefly, immunoassays often use animal antibodies (e.g. mouse, rabbit, etc.) targeting antigens of interest such as other antibodies (e.g. serology testing) or other macromolecules (e.g. viral/bacterial proteins, hormones, etc.). For infectious disease testing, immunoassay methods serve as the primary method for Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) screening. The high sensitivity and specificity of HIV/HCV immunoassay techniques are the product of decades of evolution.

During the COVID-19 pandemic, SARS-CoV-2 antigen testing appeared later, with the first FDA EUA platforms appearing in May 2020. These initial platforms used a lateral flow immunoassay (LFIA) testing format combined with a rapid POC reader. As the pandemic continued, cheaper, reader-less LFIA test cards were produced. Despite the perceived benefit of POC LFIA SARS-CoV-2 antigen tests, early supply allocations were purchased by United States Health and Human Services for use in nursing homes.

3.2. Performance against molecular techniques

Table 1B shows currently available FDA EUA POC SARS-CoV-2 antigen tests. This list is not exhaustive. Due to the lack of an FDA approved 'gold standard' for SARS-CoV-2 testing, positive percent agreement (PPA), and negative percent agreement (NPA) are used instead of sensitivity and specificity, respectively. A common trend during the COVID-19 pandemic was the significant discordance between performance reported by the FDA authorization of SARS-CoV-2 tests versus 'real world' data. The first SARS-CoV-2 antigen test receiving emergency use authorization reported 96.6% PPA and 99.3% NPA [33]. Pray et al. studied the performance of this platform against RT-PCR and reported PPA of 41.2% and NPA of 98.4% in asymptomatic persons [34]. Performance was improved in the symptomatic populations with PPA of 80.0% and NPA of 98.9%. A more recent review reported SARS-CoV-2 antigen testing to exhibit a PPA and NPA of 72.0% and 99.5%, respectively, for symptomatic patients, and 58.1% and 98.9% for asymptomatic patients [35].

Later POC SARS-CoV-2 antigen tests were achieved improved PPA and NPA. The study by Pilarowski et al. reported PPA and NPA of 93.3% and 99.9%, respectively, regardless of symptom status when using a comparative RT-PCR cycle-

Table 1. Example of emergency use authorized point-of-care COVID-19 molecular and antigen tests.

A. Molecular					
Manufacturer / Platform	**Method**	**RNA Targets**	**LoD (NDU/mL)[b]**	**PPA(%**	**NPA(%)**
Abbott POC / ID Now	Isothermal	RdRp	300000	100	100
Lucira Health / Lucira COVID-19	RT-LAMP	N	Not available	94.1	98.0
Mesa Biotech / Accula Dock	RT-PCR	N	Not available	100	100
Roche Molecular systems / cobas Liat	RT-PCR	ORF1ab/N	5400	100	100
Visby Medical / COVID-19 POC Test	RT-PCR	N1	Not available	100	95.3
B. Antigen Assays					
Manufacturer / Platform	**Method**	**Ag Targets**	**LoD (TCID50/mL)**	**PPA(%)**	**NPA(%)**
Abbott Diagnostics / BinaxNow COVID-19 Ag	ICMA	N	140.6	84.6	98.5
AccessBio / CareStart COVID-19 Ag	ICMA	N	6.4×10^3	83.3	100.0
Becton Dickenson / Veritor	IMCA	N	1.4×10^2	84.0	100.0
Ellume Limited / Elumme COVID-19 Home	LFIA	N	$1.0 \times 10^{3.8}$	91.0	96.0
Lumira Dx / LumeriaDx SARS-CoV-2 Ag test	LFIA	N	2.8×10^5	97.6	96.6
Quidel / Sofia-2	LFIA	N	3.4×10^5	96.7	100.0

Notes: [a]A complete list is available from the FDA emergency use authorization website: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas; [b]LoDs based on comparisons using the FDA reference panel.
Abbreviations: ABI, Applied Biosciences; Ag, antigen; CDC, Centers for Disease Control and Prevention; ddPCR, digital droplet PCR; E, envelope protein gene; IMCA, immunochromographic membrane assay; LAMP, loop-mediated isothermal amplification; LFIA, lateral flow immunofluorescent assay; LoD, limit of detection; N, nucleoprotein gene; NDU, nucleic acid test detectable units; NPA, negative percent agreement; ORF, open reading frame; PCR, polymerase chain reaction; PPA, positive percent agreement; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid; RT, reverse transcription; TCID50, median tissue culture infective dose; TMA, transcription mediated amplification.

threshold (Ct) value of <30 as a cut off [36]. The rationale for using a Ct cut off when comparing SARS-CoV-2 antigen testing versus molecular approaches is controversial since it is not established at what Ct-value representing viral RNA load is disease producing and/or infectious. As such, Prince-Guerra et al., using the same POC SARS-CoV-2 antigen test and compared against RT-PCR without a Ct-value cut off reported a far lower PPA (35.8%) and NPA (99.8%) in asymptomatic individuals [37].

4. SARS-CoV-2 testing best practices

As of this review article, the Centers for Disease Control and Prevention (CDC) provides guidance on testing of individuals with and without symptoms [38]. Briefly, for symptomatic patients (high pretest probability), positive SARS-CoV-2 antigen results are assumed to be real and do not require confirmation by molecular methods. Antigen negative results in symptomatic individuals should be followed up by molecular testing. For asymptomatic populations, the CDC differentiates those with close contact with COVID-19 versus those with no known exposure. Asymptomatic individuals that have close contact with COVID-19 and testing antigen positive may require confirmation by molecular approaches. Expanding further, the Infectious Disease Society of America recommends confirmation of all antigen negative results; whereas, the CDC currently supports the notion that a negative is considered sufficient for rule out. Asymptomatic individuals with unknown exposure status are tested similarly [39].

5. Considerations for testing and clinical utility of POC tests for COVID-19 in the ED

When selecting a COVID-19 test for use as a POC test in the ED, health systems should consider a number of factors as there are many tests that are FDA-authorized for the POC setting with each test only being authorized for certain specimen types. Collection of the proper specimen that is on-label for the POC test is essential to maintaining regulatory compliance. Beyond obtaining the proper specimen, it is also essential specimens are collected using swabs and transport media that are authorized for use with the test. This can be quite challenging during a pandemic as health systems have been forced to diversify their suppliers and inventory can change daily. CLIA test complexity is also a factor. Although emergency medicine personnel can operate waived and moderate complexity tests, the latter carries additional logistical burden which may limit who can operate the devices, and also brings in additional requirements such as proficiency testing. To this end, devices that are considered 'waived' are more easily deployed in the ED setting [40].

The safety of healthcare workers is also an essential consideration when testing in the ED, for personnel who are handling specimens, the CDC recommends standard precautions plus a face mask be implemented. For personnel who are working with specimens and collecting specimens the CDC recommends eye protection, gloves, gowns, and an N95 or high-level respirator [37]. Appropriate training of ED testing personnel, proficiency testing of all test operators, quality control, decontamination of instruments, and the testing environment are also essential to a successful ED testing program.

COVID-19 is rapidly spreading particularly with the emergence of several new variants [41] – requiring continued surveillance by sequencing or other means [38]. Despite significant efforts, the diagnosis of COVID-19 remains challenging. In particular, overuse of antibiotics for patients with COVID-19 is especially concerning given the rise in antimicrobial resistance. A recent study of antibiotic prescribing during COVID-19 in South Korea found that 35% of 6871 patients received antibiotics. Eight percent received anti-MRSA or anti-pseudomonal agents, and this was more common in

those with severe illness. Also concerning was the use of broad-spectrum antibiotics, including fluoroquinolones, third-generation cephalosporins, and macrolides. Importantly the investigators could not confirm bacterial co-infection, leading to concerns about potential collateral damage including patient adverse events due to unnecessary antibiotics and downstream antibiotic resistance [42]. A study in Spain documented a 320% increase in the use of azithromycin from January 2019 to March 2020, with an overall increase in antibiotic use by 11.5% in March 2020 compared to the prior month [43]. Access to rapid diagnostics is one of the cornerstones of the IDSA's approach to combatting antimicrobial resistance [44].

Rapid testing for SARS-CoV-2 in the ED can facilitate earlier diagnosis, and appropriate isolation precautions as well as lead to more timely contact tracing of exposed contacts. PCR is the primary approach to diagnosis in ED settings, given the high accuracy needed for appropriate initiation of COVID-specific therapies in eligible patients as well as reducing unnecessary antimicrobial therapy particularly in the setting of COVID-19 pneumonia where secondary bacterial infection or bacterial co-infection is not suspected [45].

A recent meta-analysis suggests bacterial co-infection is uncommon, occurring in 3.5% of patients, but ranges from 0% to 45%. Secondary bacterial infection in the setting of COVID-19 is also infrequent, occurring in an estimated 14% of patients and is more common in critically ill patients [46]. The majority of patients with COVID-19 received antibiotics (71.9%, 95%CI 56.1 to 87.7%). A limitation of the study was that a variety of methodologies were used to detect the presence of bacterial infections [46]. Given the low prevalence of bacterial co-infection in COVID-19, rapid diagnosis of COVID-19 could facilitate antimicrobial stewardship strategies.

Current limitations in the diagnosis of acute infections are that clinical judgment for infectious disease diagnosis is insensitive and nonspecific and current diagnostic technology often fails to provide rapid and accurate data, leading to a conservative management approach where clinicians err on the side of antibiotic overuse, both in terms of empiric therapy as well as spectrum. This increases in turn not only downstream antibiotic resistance but the likelihood of patient-specific adverse events, including *Clostridioides difficile* infection [47].

In addition, there are specific challenges to the implementation of POC tests in the ED, including alignment with workflow in a busy environment. Additional factors to consider are that clinicians work in shift-based scheduling formats, the need for quick decision-making often with limited clinical or diagnostic information. Clinicians also describe concerns around diagnostic uncertainty and the potential for poor patient outcomes especially in safety-net settings where patients may not have access to follow up primary or specialty care [48]

Emergency Department POC tests should demonstrate high sensitivity and specificity especially for high-risk conditions like COVID-19 [15]. Rapid molecular POC for other conditions such as influenza and group A strep can facilitate avoidance of unnecessary POC as long as the concept of positive and negative predictive value is understood by the clinician [49]. Ideally, turn around time (TAT) should be less than 30 minutes for most conditions, understanding that actual TAT is longer than laboratory TAT, and there is no one size fits all approach to deciding on POC testing implementation [50]. In some cases, logistic and regulatory considerations may lend themselves to a laboratory-based approach particularly for academic EDs versus a decentralized approach that may be beneficial to urgent care or freestanding facilities. Tests should be easy to perform and simple to interpret [51].

6. Gaps in current testing

One of the major gaps in the diagnosis of COVID-19 is the use of both molecular and antigen detection of SARS-CoV-2 does not take into account the host response [52]. Furthermore, the detection of bacterial co-infection and superinfection remains a challenge as many syndromic panels do not include many bacterial targets and lower respiratory tract specimens are more difficult to obtain than upper respiratory tract specimens. Challenges to POC testing implementation for SARS-CoV-2 testing in the ED include continued concerns for supply chain issues in the case of molecular tests, as well as issues with other supplies such as specimen collection supplies and media [53]. An additional consideration is POC testing for symptomatic versus asymptomatic screening. Persons who are asymptomatic with COVID-19 may have viremia below the limit of detection for POCT, and the timing of specimen collection is key [54].

While there is great potential for rapid and accurate POCT to decrease unnecessary empiric antibiotic use, provide early therapies, and decrease transmission, alignment with clinical workflows and clinician heuristics may necessitate a workflow assessment as well as consideration of behavioral approaches including engineering choices through the electronic health record (EHR) to promote diagnostic as well as antimicrobial stewardship including antiviral and other COVID-19 treatments [55,56]; Many studies have failed to show the desired impact on clinical care and outcomes [57,58]. This is likely due to limitations of testing in dynamic complex healthcare environments. The major gap remains the integration of clinical microbiology and healthcare setting workflows, the failure to consider heuristics and challenges to changing clinical decision-making behavior, and the need for integration of testing and clinical management with clinical decision support [59].

7. Expert opinion

A paradigm shift is underway, led by the development and implementation of POC technologies in the ED and other acute care settings. Novel diagnostics integrated with antimicrobial stewardship strategies and clinical decision support systems may facilitate early targeted antibiotic treatment supplanting empiric broad-spectrum antibiotic use. This in turn should lead to improved outcomes and decreased adverse events for patients as well as a downstream public health

benefit of stemming the emergence and acceleration of antibiotic-resistant organisms.

There remain numerous unexplored areas in point-of-care testing for patients suspected to have COVID-19 as well as for screening of asymptomatic individuals for public health, employment, or travel purposes among others. For example, there is much wider availability of over-the-counter testing at this stage of the pandemic. Multiple platforms are currently available for patients or employers to purchase for individual use without seeing a healthcare provider or encountering the healthcare setting. Some examples include BinaxNow and Ellume, which can also be purchased through online vendors for delivery to someone's home without stepping into a retail venue such as a pharmacy. While this provides greater access to testing, it remains to be seen the role these tests will fill as well as performance in the hands of non-laboratory or healthcare professionals, and without the opportunity for public education on the use and limitations of these tests. In some cases, patients are presenting to the ED for confirmation of results and requests for treatment. With appropriate education of the public one important question is whether these tests might offload the volume of patients including the worried well presenting to the ED. In addition, there remains a need for performance and standardization of these tests especially as new variants emerge.

Another area for future research is the need to determine the clinical significance of RNA viral load and antigen positivity as it relates to infectivity and potential transmission. Prognostic tools for disease severity have limited value, and it is still unclear how RNA viral load and test positivity might predict an individual's prognosis and progression to more severe disease including hospitalization, mechanical ventilation, and death. It is likely that additional tools such as host response markers and machine learning will provide additional insight into these important questions.

Finally, there is a critical need for research to determine clinical utility and recommendations for SARS-CoV-2 testing in asymptomatic versus symptomatic individuals at the point of care. This research in turn could inform improved and more coherent local and national strategies for the use of both molecular and antigen tests at the point of care in the ED and other settings. There are important workflow considerations for the use of POC testing in acute episodic care settings, as well as addressing clinician uptake and use of these tests to impact the patient experience and clinical outcomes.

In summary, point-of-care testing for SARS-CoV-2 is a dynamic and exciting area for innovation in healthcare delivery and research. Successful development and implementation and evaluation of these tests could provide an important model for response to future pandemics.

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