COVID-19 rapid diagnostics: practice review

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ABSTRACT

Point-of-care tests for SARS-CoV-2 could enable rapid rule-in and/or rule-out of COVID-19, allowing rapid and accurate patient cohorting and potentially reducing the risk of nosocomial transmission. As COVID-19 begins to circulate with other more common respiratory viruses, there is a need for rapid diagnostics to help clinicians test for multiple potential causative organisms simultaneously.

However, the different technologies available have strengths and weaknesses that must be understood to ensure that they are used to the benefit of the patient and healthcare system. Device performance is related to the deployed context, and the diagnostic characteristics may be affected by user experience.

This practice review is written by members of the UK's COVID-19 National Diagnostic Research and Evaluation programme. We discuss relative merits and test characteristics of various commercially available technologies. We do not advocate for any given test, and our coverage of commercially supplied tests is not intended to be exhaustive.

INTRODUCTION

Human infection with the novel coronavirus SARS-CoV-2 was first reported in December 2020.[1] Since then, it has caused a global pandemic forcing the reorganisation of healthcare systems around the world. The pandemic has placed unprecedented strain on Emergency Departments (ED), which have had to rapidly learn to triage, diagnose and treat a new disease. Nosocomial spread in hospitals has also been a cause for concern.[2] The ability to rapidly detect SARS-CoV-2 in patient samples would enable EDs to rapidly differentiate between patients who have COVID-19 and those who do not. This would enable isolation of those who are infected without overusing resources and likely reduce the risk of nosocomial transmission.

The reference standard for diagnosing SARS-CoV-2 was quickly established as reverse transcriptase PCR (RT-PCR) from a nasopharyngeal and/or oropharyngeal swab.[3] Unfortunately, the long turnaround time for RT-PCR testing (typically >12 hours) means that this method cannot be relied on to inform timely decision making in the ED. Some healthcare providers have therefore developed intermediate cohorting strategies based on clinician gestalt, or imaging, whereby patients are referred to low, uncertain and high risk wards.[4 5] Rapid diagnostic tests could aid such decision making in the ED. In this review, we explore the current literature and issues to be considered when implementing existing technologies.

THE CLINICAL NEED FOR RAPID DIAGNOSTIC TESTS

A survey of unmet needs for COVID-19 tests in UK health and social care settings[6] carried out in June 2020 found that hospitals identified COVID-19 testing as the second highest unmet need, with the greatest priority being a test for symptomatic patients presenting to hospitals for infection control. However, there is also a need for testing asymptomatic patients being admitted to hospital for a reason other than COVID-19 (ie, elective procedures).

Real estate within hospitals changed significantly during the course of the pandemic to support cohorting of patients based on their COVID-19 status to prevent within-hospital transmission.[7 8] In general, these areas can be split into high risk (positive COVID-19 diagnosis), intermediate (pending COVID-19 diagnosis) and low risk (negative COVID-19 diagnosis).[9] An important use case for rapid COVID-19 tests would therefore be to test all admitted patients to aid appropriate use of isolation and cohorting beds.

Without rapid testing, cohorting is usually based on clinical suspicion of COVID-19 status, while waiting on the results of laboratory RT-PCR tests. This may mean that all patients with symptoms compatible with COVID-19 are cohorted together (risking the possibility that some will not have COVID-19 but and could then become infected) or that decisions are guided by unstructured (and untested) clinical judgement combining symptoms, physical and radiological findings and history of exposure. With rapid testing modalities for COVID-19 now more readily available, results of these tests can be used to support clinical decision making and potentially reduce inappropriate cohorting and nosocomial transmission. However, it is generally accepted that there is a trade-off between rapidity of results and accuracy. Circumstances of the hospital and disease prevalence may determine what is acceptable in terms of accuracy of a rapid test for SARS-CoV-2.

MINIMUM ACCEPTABLE TEST CHARACTERISTICS

The minimum required accuracy for a rapid SARS-CoV-2 test will depend on the prevalence of COVID-19 and the downstream actions and consequences following different test results. For example, a patient with COVID-19 who tests negative (false negative) and is moved to a non-COVID-19 ward

		False Negatives	
		Sensitivity 70%	Sensitivity 80%
Prevalence	10%	30	20
	20%	60	40
	40%	120	80

		False positives	
		Specificity 95%	Specificity 99%
Prevalence	10%	45	9
	20%	40	8
	40%	30	6

Figure 1 Absolute numbers of false negatives and positives in a theoretical sample of 1000 patients with varying diagnostic characteristics and prevalence.

could expose other patients and staff unnecessarily to COVID-19, potentially resulting in an outbreak. Conversely, a patient without COVID-19 who tests positive but does not have the disease and is cohorted in a COVID-19 ward results in unnecessary exposure for that individual.

In high prevalence scenarios, such as acute admissions, it only takes a small drop in sensitivity for a clinically significant number of false negative results to occur. For example, in a high prevalence setting (40%), a drop in test sensitivity from 80% to 70% results in 40 more false negative results per 1000 patients (figure 1). In a lower prevalence setting (10%), this effect is lessened, with only 10 additional false negatives. Of course, even one false negative wrongly cohorted could cause nosocomial transmission, the 'grenade in the haystack'. However, the absolute number of false positives increases from 6 to 9 as the prevalence drops from 40% to 10%. If these false positive patients are admitted to a COVID-19 ward, they may become infected and then test positive (true positive), 'the hidden vulnerable'.

Minimum standards for SARS-CoV-2 tests were developed early in the pandemic; the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the WHO published target product profiles (TPPs) for novel COVID-19 diagnostics.[10 11] TPPs are documents that outline the acceptable and desirable characteristics for a new test to guide industry on what is needed to meet a specific, unmet clinical need.[12] The current MHRA version of the TPP for a point-of-care SARS-CoV-2 detection test recommends a desired diagnostic sensitivity of at least 97% (acceptable 80%) and desired diagnostic specificity of 99% (acceptable 95%).[10] The UK's National Institute for Health and Care Excellence has conducted economic modelling to explore the potential cost-effectiveness of a test that meets the MHRA TPP criteria,[13–15] in line with recently published recommendations.[16]

The UK government commissioned the Technologies Validation Group (TVG) to evaluate SARS-CoV-2 additional diagnostics. The TVG conducted a protocolised evaluation of a variety of different technologies, using contrived samples (artificial) to look at analytical performance and swabs from symptomatic patients that were run in laboratory and ED environments to look at clinical performance.

TYPES OF TESTS
RT-PCR testing
PCR is a process to amplify specific regions of a genome; the samples require preparation prior to being processed. Primers enable PCR to target and amplify specific targets; the enzyme reverse transcriptase binds the primers to the genome. The procedure can be run on the raw clinical sample (direct), or

an additional step can be included to separate the target cells from the clinical samples (indirect). Subsequently, PCR includes a series of thermal cycles that progressively amplify the target genome. A positive result can become detectable after a number of cycles; this is known as the cycle threshold (Ct). The higher the Ct, the more thermal cycles (amplifications) that were required to detect the target. It can therefore be inferred that the more amplifications required (thermal cycles), the lower the original amount of target genomic material in the sample. This has been used to estimate the viral load, with a lower Ct value indicating a higher viral load.[17] Unfortunately, this estimation may not be reliable, with a 100-fold variation previously noted depending on device and users.[18 19]

RT-PCR testing of oropharyngeal or nasopharyngeal swabs is the current reference standard for the detection of current for SARS-CoV2 infection. Recommendations differ for which anatomical area of the upper respiratory tract that is to be swabbed, ranging from nasopharyngeal to anterior turbinate. However, while there are obvious benefits to the patient's experience, each technology is validated with a specific anatomical area swabbed and should be implemented accordingly. The time-to-test result for an RT-PCR test is typically 6–8 hours,[20] which leaves EDs with the challenge of how to cohort patients at the front door who require urgent care. Another issue with RT-PCR is the inaccuracy in describing the viral load of a sample. Digital PCR is an emerging second to the current reference standard; the process differs from traditional PCR as the sample is divided into tens of thousands of aliquots and a fluorescence reading is taken per aliquot rather than one reading per sample. This enables the viral load of the sample to be accurately quantified,[21] thereby enabling more accurate assertions to be made regarding diagnostic characteristics in different viral loads.

Direct molecular versus antigen detection
A variety of direct technologies have been developed to rapidly detect SARS-CoV-2 infection. These differ from indirect technologies in their ability to handle unprocessed clinical swabs without additional extraction steps. This can enable these technologies to be point of care (POC) or near POC. They can be broadly divided into two categories: molecular and antigen direct detection technologies. Molecular technologies seek to identify SARS-CoV-2 by detection of viral genetic material, while antigen detection identifies the pathogen's protein antigens. Molecular technologies amplify the amount of genetic material by using PCR, loop-mediated isothermal amplification (LAMP) or other amplification and detection techniques. Because these technologies typically amplify small amounts of genetic material from the SARS-CoV-2 virus, they have the potential to be very sensitive.

Antigen detection technology	Direct-molecular detection technology
Cheap per unit cost	Expensive processing units
Rapidly scalable manufacturing	
Likely lower sensitivity	Likely maintains higher sensitivity
Satisfactory specificity	
One at a time testing*	
Minimal training and testing steps	
Likely lower sensitivity with less experienced users	

Figure 2 Strengths and weaknesses of each detection technology. *Some direct molecular technologies allow batch testing.[20] Of note, neither technology class has the proven ability to quantify viral load reliably.

However, they can be more expensive, and they typically have longer turnaround times than antigen detection techniques (figure 2). Antigen detection technology is, broadly, fast, simple and cheap. However, it may be more challenging to achieve a comparable sensitivity to RT-PCR.

Antigen detection technologies come in a variety of forms, from the simple pregnancy test style lateral flow devices with or without a digital reader, to micro fluidic immunofluorescence assays that run with analysers that may be portable or bench top. The simplest form is cheap and available at scale; however, this may be to the detriment of preferred diagnostic characteristics.[22]

Lateral flow devices
Lateral flow devices are hand-held antigen detection devices that use swabs or saliva samples to return a result quickly, often within 15 min. A widely studied later flow device (Innova) has been reported to have a sensitivity of 40.0%–79.0% and specificity of 99.9% in two large-scale studies.[23 24] One of these studies focused on asymptomatic community testing centres,[24] while the other involved rapid recruitment of symptomatic positive cases at community testing centres (within the Facilitating Accelerated Clinical Validation of Novel Diagnostics for COVID-19 (FALCON C-19) study) and recruitment of PCR-negative individuals in a variety of hospital/community settings.[23] The FALCON study also found the sensitivity of the Abbott Panbio lateral flow test to be 74% (95% CI 64% to 82%), whereas the Orientgene test had a sensitivity of 82% (95% CI 73% to 89%) and Deepblue had a sensitivity of 73% (95% CI 66% to 79%).[23]

The sensitivity of lateral flow devices appears to increase with lower Ct values. At Ct values ≤25, the sensitivity of the Innova test reached 95.0%.[23] This may infer that the sensitivity improves with higher viral loads.

Because of their imperfect sensitivity, lateral flow devices may not be acceptable to 'rule out' COVID-19 in patients who are symptomatic. Instead, they have been used to screen for asymptomatic cases in the general population. This is an innovative approach to testing, which is largely unsupervised by health professionals. As such, it has sparked debate.[23 25] This use case relies on the principle that asymptomatic individuals would not otherwise undergo testing for COVID-19. By testing frequently used lateral flow devices, a proportion of asymptomatic or presymptomatic cases of COVID-19 will be identified early,

enabling rapid isolation and limiting spread. Furthermore, as sensitivity of lateral flow tests is high for patients with the highest viral loads, those who are most likely to transmit the infection to others are likely to be identified through regular testing.

When used in an asymptomatic population, Public Health England surveillance data have estimated that the false positive rate is less than one in a thousand, consistent with the findings in studies.[26] As the diagnostic accuracy of a test is dependent on the prevalence and severity of disease within the target population,[15] prior to deployment in emergency care settings, we still require evidence for the accuracy of lateral flow testing in that context, and how the results should influence clinical decisions remains to be defined. At present, the evidence does not support the use of lateral flow devices to exclude SARS-CoV-2 infection (rule-out), there is a possibility that it could be used to 'rule-in' the diagnosis.[25]

In December 2020, NHS England published a standard operating procedure for lateral flow testing for ED patient pathways where other forms of rapid testing are not available.[27] Lateral flow testing is recommended for use in combination with RT-PCR testing to facilitate immediate action in ED for those with positive lateral flow results. As such, they were not used for any definitive diagnosis. Instead, the hybrid testing pathway was used to cohort ED patients and enable a risk-stratified pathway.

Complex antigen detection devices
The LumiraDx Antigen test is a complex antigen device using a microfluidic immunofluorescence assay on anterior nasal swabs. The small desktop device can generate a result within 12 min, with minimal sample preparation.[28] The sensitivity estimates range from 83.8% (95% CI 76.4% to 89.2%) in the TVG report to 97.6% (95% CI 91.6% to 99.3%) in another study, with consistently high specificity of 96.6%–98.7%.[29 30]

Direct molecular detection
Direct molecular diagnostic technology sits in a middle ground between antigen detection and laboratory based qRT-PCR in terms of diagnostic characteristics and complexity.

The Abbott ID NOW COVID-19 assay uses isothermal nucleic acid amplification, similar to PCR. The ID NOW device can provide results within 10 min. The TVG, in the context of hospital evaluation of symptomatic patients, demonstrated a sensitivity and specificity of 93.2% (95% CI 84.3% to 97.5%) and 98.4% (95% CI 96.5% to 99.3%).[31] However, four other studies including a total of 222 cases demonstrated a sensitivity of 73.0% (95% CI 66.8% to 78.4%) with 99.7% (95% CI 98.7% to 99.9%) specificity.[22]

The TVG also reviewed a direct LAMP assay from OptiGene RT-LAMP using samples from symptomatic patients in the community and hospital. This assay demonstrated a sensitivity of 72% (95% CI 0.64 to 0.78) for nasal swabs, which improved to 80% (95% CI 0.72 to 0.85) when saliva was used. The indirect (non-POC) version, like laboratory RT-PCR assays, had more favourable diagnostic characteristics, with a sensitivity and specificity of 95% (95% CI 0.91 to 0.97) and 99% (95% CI 0.99 to 1.00).[32 33]

Different companies have attempted to develop and validate POC (or near POC) rapid direct RT-PCR technologies. Of the POC technologies, direct RT-PCR has the potential for impressive diagnostic characteristics with run times shorter than traditional PCR. DNANudge, POCKIT and SAMBA II all have comparatively simple sample preparation. The TVG reported the sensitivity for DNANudge's COVIDNudge at 82.1% (95%

Table 1 Diagnostic characteristics for SARS-CoV-2 rapid diagnostics – results are reported as published

Technology	Population	Sensitivity % (95% CI)	Specificity % (95% CI)	Turnaround time
Antigen detection† (pooled)[22]		**72.0 (63.7 to 79.0)**	**99.5 (98.5 to 99.8)**	
Panbio[23 43]	Mixed	74.5 (69.9 to 78.7)	99.7 (99.3 to 99.9)	15 min
BinaxNow[44 45]	Symptomatic hospital patients	74 (64 to 82)	99.9 (97 to 100)	15 min
Innova†[23 24 46]	Asymptomatic	40.0 (28.5 to 52.4)	99.9 (99.8 to 99.99) :	20 min
	Symptomatic cohort	Lab scientists running tests, 79.0 (72 to 84); healthcare workers running tests, 70.0 (73 to 76)	99.7 (99.5 to 99.8)	
LumiraDx SARS-CoV-2 antigen test[30]	Symptomatic hospital patients	83.8 (76.4 to 89.2)	97.6 (91.6 to 99.3)	12 min
Direct molecular test† (pooled)[22]		**95.1 (90.5 to 97.6)**	**98.8 (98.3 to 99.2)**	
OptiGene (saliva)[32 33]	**Mixed**	80 (72 to 85)	100 (0.99 to 1.00)	**20 min**
Abbott ID Now SARS-CoV-2[22 31 47]	Symptomatic hospital patients	Meta-analysis: 73.0 (66.8 to 78.4) TVG evaluation: 93.2 (84.3 to 97.5)	Meta-analysis: 99.7 (98.7 to 99.9)[22] TVG evaluation: 98.4 (96.5 to 99.3)	13 min
RT-PCR				
DNANudge COVID-19[34 48]	Symptomatic hospital patients	82.1 (77.7 to 85.7)	99.1 (98.4 to 99.5)	90 min
Horiba POCKIT SARS-CoV-2[49]	Symptomatic hospital patients	95.7 (91.0 to 98.1)	97.7 (95.2 to 99.0)	85 min
SAMBA II SARS Co-V-2 test[35]	Symptomatic hospital patients	98.8 (NR)	100 (NR)	90 min

This seeks to be a list that is representative but not comprehensive; inclusion here is not an endorsement. The studies cited for diagnostic characteristics are from the UK's TVG, published CONDOR evaluations and a Cochrane review. This table summarises data from studies with different methodologies including lab reviews and in context evaluations; it is not a complete review of all available literature. The FIND collaborative maintains a tracker of all available technologies available here https://wwwfinddxorg/covid-19/pipeline/.

*The Innova lateral flow test is currently one of the most studied in part due to its widespread deployment in the UK. The reported sensitivity varies; we report the range found in the published literature.

†Pooled data is referenced from the Cochrane review by Dinnes et al [22]

CONDOR, COvid-19 National DiagnOstic Research and evaluation; NR, not reported; TVG, Technologies Validation Group.

CI 77.0% to 85.7%) and for SAMBA II it reported a sensitivity of 98.8% in comparison to RT-PCR[34 35] (see table 1).

LESSONS LEARNT SO FAR ABOUT EVALUATION/IMPLEMENTATION

In July 2020, we commenced the COvid-19 National DiagnOstic Research and evaluation (CONDOR) programme, a platform designed to evaluate multiple diagnostic tests for COVID-19. CONDOR incorporated two prospective, multicentre studies. The RApid community Point of care Testing fOR COVID-19 (RAPTOR-C19) study focused on validation of new tests in community settings, while the FALCON C-19 study primarily validates COVID-19 tests in secondary care settings, focusing largely on the ED. The CONDOR programme also provides analytical validation of new tests, defines care pathways, evaluates human factors and usability associated with new COVID-19 tests and incorporates important patient and public involvement. To date, 7847 patients have been recruited to CONDOR from 129 sites, enabling the validation of more than 26 new tests for COVID-19.[36]

In context evaluation

Our experience within the CONDOR programme has highlighted some common pitfalls in the evaluation of new tests for COVID-19. To avoid overestimating diagnostic accuracy, it is critically important to evaluate the diagnostic accuracy of the tests 'in context', that is, when used exactly as they would be in real-world clinical practice in the hands of the end user, on the target population.[37] For example, the sensitivity of lateral flow devices appears to be higher when used by healthcare professionals and laboratory scientists, but it may be substantially lower when used by less qualified individuals.[25 38] Lateral flow devices, arguably some of the simplest technologies, have demonstrated a 20% drop in sensitivity between experienced and inexperienced user groups.[38] The usability of the assay is important as it may be susceptible to common user errors or deviations from the manufacturer's instructions.

Biosafety

Biosafety is an important consideration, noting that we are trying to detect a pathogen that has caused a global pandemic. The action of pipetting, mixing and analysing can generate aerosols and disperse the sample of potentially live virus.[39] This risk can affect the deployment of the technologies; if a system widely disperses the sample, then it may need to be run within a negative pressure environment (laboratory safety cabinet). This may not be cost-effective nor practical to fit in a busy ED. If in processing samples the novel technology is deemed to have a splash risk with live virus than while a safety cabinet may not be necessary, full PPE and suitable location in the ED environment will likely be required.

Communication

A key challenge has been the communication of the results of different tests with different diagnostic characteristics to patients. In such circumstances, early communication and an understanding of the patient's baseline knowledge is key (figure 3).

SUMMARY OF PROGRESS AND FUTURE DIRECTIONS

The global response to the COVID-19 pandemic has seen the accelerated development of numerous novel diagnostic technologies that can assist with the rapid detection of SARS-CoV-2. Rapid throughput analysers have enabled RT-PCR to be run relatively rapidly and at scale, providing a reference standard method for diagnosis of COVID-19 in hospitals and facilitated the set-up of community testing centres. Numerous POC testing technologies have also been developed using a variety of methods. Many of those are suitable for use in EDs.

	Moderate sensitivity and high specificity test e.g. antigen tests	High sensitivity and high specificity test e.g. molecular tests
Establish the patient's prior knowledge	What do you know about lateral flow tests?	Have you heard of any tests for COVID-19 that are like PCR?
Sharing the plan in advance		This rapid COVID-19 test is similar to the gold standard slower laboratory PCR test
Positive result	If the test result is positive we can be reasonably sure you have the COVID-19	If the test is positive we can be confident that you have COVID-19
Negative result	If the test result is negative then we don't have any new information and we are none the wiser as to your COVID-19 status. If we want to find out more information we will need to do a more accurate but slower laboratory PCR test	If negative we can also be confident that you do not have COVID-19.

Figure 3 Communication pearls for conveying the results of novel COVID-19 diagnostic tests.

While POC diagnostics could be used to expedite clinical decision making, some important challenges remain. First, independent evaluations have shown that none of the available POC tests have sufficiently high sensitivity to rule out the diagnosis of COVID-19 in symptomatic individuals. An important goal of future work should therefore be to identify a structured way to rapidly 'rule out' COVID-19 for patients attending the ED, potentially combining the results of rapid POC tests with other clinical information (eg, symptoms, physiological parameters or imaging results).

It would also be valuable to enhance our understanding of the association between viral load and infectivity. It is clear that rapid antigen tests are more likely to return false negative results in patients later in the disease process, who may be less infectious.[40] If research can demonstrate that patients for whom virus cannot be detected with rapid antigen tests are highly unlikely to transmit COVID-19 to others, then the tests could be used to safely triage patients to non-COVID-19 areas or to enable individuals to be released from self-isolation. With serial testing, the sensitivity of the tests may also be expected to increase, but to our knowledge, this is yet to be evaluated in a real-world setting. A UK government modelling report theorised that serial testing would likely reduce transmission at a population scale, but significant uncertainty remains.[41]

Furthermore, we still do not completely understand the effects of human and behavioural factors on the results obtained from rapid tests for COVID-19. For example, the accuracy of lateral flow tests when used for mass self-testing in the general population is yet to be fully evaluated.

It will also be important for future research to verify the accuracy of the currently available diagnostic tests for variants of concern. Future evaluations should verify that the performance of tests is maintained for COVID-19 variants, while further iterations of POC tests may be more robust in detecting new variants (eg, by targeting more than one SARS-CoV-2 gene or antigen). Variant detection can be checked in silicon for molecular assays and using protein checking for antigen tests, potentially negating the need for wet testing the assay.

The lifting of non-pharmaceutical interventions also allows otherwise endemic respiratory viruses to recirculate, and this has led to predictions of surges in respiratory syncytial virus infections.[42] As such, multiplex testing will be an important priority for the forthcoming winter, when other respiratory viruses with overlapping symptomology may become more prevalent.

CONCLUSION

Rapid COVID-19 diagnostics are an appealing concept that can potentially aid with triage and prevention of nosocomial spread. However, the plethora of available technology at different stages of validation makes the landscape confusing. This is made more complicated as the diagnostic characteristics are being affected by the environment they are in.

The future for this technology is exciting with the potential for it to benefit patient care, but careful observation and evaluation will be required while it remains in its infancy.

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