




# COVID-19 rapid diagnostics: practice review

Charles Reynard <sup>1,2</sup>, Joy A Allen <sup>3,4</sup>, Bethany Shinkins,<sup>5</sup> Graham Prestwich,<sup>6</sup> Johnathan Goves,<sup>2</sup> Kerrie Davies,<sup>7,8</sup> Richard Body <sup>1,2</sup> on behalf of the CONDOR group

**Handling editor** Katie Walker

<sup>1</sup>Emergency Department, Manchester University NHS Foundation Trust, Manchester, UK

<sup>2</sup>Division of Cardiovascular Sciences, The University of Manchester, Manchester, UK

<sup>3</sup>NIHR Newcastle In Vitro Diagnostics Co-operative, Translational and Clinical Research Institute, Newcastle University School of Clinical Medical Sciences, Newcastle University, UK

<sup>4</sup>Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK

<sup>5</sup>Test Evaluation Group, Leeds Institute for Health Sciences, University of Leeds, Leeds, UK

<sup>6</sup>Patient and Public Involvement, Yorkshire and Humber Academic Health Science Networks, Leeds, UK

<sup>7</sup>Healthcare Associated Infections Research Group, University of Leeds, Leeds, UK

<sup>8</sup>NIHR Leeds In Vitro Diagnostics Co-operative, University of Leeds, Leeds, UK

## Correspondence to

Dr Charles Reynard, Emergency Department, Manchester University NHS Foundation Trust, Manchester, Greater Manchester, UK; [charlie.reynard@nhs.net](mailto:charlie.reynard@nhs.net)

Received 5 July 2021

Accepted 27 October 2021



© Author(s) (or their employer(s)) 2021. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Reynard C, Allen JA, Shinkins B, *et al.* *Emerg Med J* Epub ahead of print: [please include Day Month Year]. doi:10.1136/emmermed-2021-211814

## 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4,5</sup> 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<sup>6</sup> 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.<sup>7,8</sup> 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).<sup>9</sup> 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 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.<sup>10 11</sup> 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.<sup>12</sup> 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%).<sup>10</sup> 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,<sup>13–15</sup> in line with recently published recommendations.<sup>16</sup>

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.<sup>17</sup> Unfortunately, this estimation may not be reliable, with a 100-fold variation previously noted depending on device and users.<sup>18 19</sup>

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,<sup>20</sup> 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,<sup>21</sup> 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.<sup>20</sup> 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.<sup>22</sup>

### 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 lateral 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.<sup>23 24</sup> One of these studies focused on asymptomatic community testing centres,<sup>24</sup> 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.<sup>23</sup> 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%).<sup>23</sup>

The sensitivity of lateral flow devices appears to increase with lower Ct values. At Ct values  $\leq 25$ , the sensitivity of the Innova test reached 95.0%.<sup>23</sup> 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.<sup>23 25</sup> 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.<sup>26</sup> As the diagnostic accuracy of a test is dependent on the prevalence and severity of disease within the target population,<sup>15</sup> 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.<sup>25</sup>

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.<sup>27</sup> 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.<sup>28</sup> 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%.<sup>29 30</sup>

### 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%).<sup>31</sup> 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.<sup>22</sup>

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).<sup>32 33</sup>

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 |
|-----------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------|
| <b>Antigen detection† (pooled)<sup>22</sup></b>     |                               |                                                                                                  |                                                                                         |                 |
| <b>72.0 (63.7 to 79.0)</b>                          |                               |                                                                                                  |                                                                                         |                 |
| Panbio <sup>23 43</sup>                             | Mixed                         | 74.5 (69.9 to 78.7)                                                                              | 99.7 (99.3 to 99.9)                                                                     | 15 min          |
| BinaxNow <sup>44 45</sup>                           | Symptomatic hospital patients | 74 (64 to 82)                                                                                    | 99.9 (97 to 100)                                                                        | 15 min          |
| Innova <sup>23 24 46</sup>                          | 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 <sup>30</sup>      | Symptomatic hospital patients | 83.8 (76.4 to 89.2)                                                                              | 97.6 (91.6 to 99.3)                                                                     | 12 min          |
| <b>Direct molecular test† (pooled)<sup>22</sup></b> |                               |                                                                                                  |                                                                                         |                 |
| <b>95.1 (90.5 to 97.6)</b>                          |                               |                                                                                                  |                                                                                         |                 |
| OptiGene (saliva) <sup>32 33</sup>                  | Mixed                         | 80 (72 to 85)                                                                                    | 100 (0.99 to 1.00)                                                                      | <b>20 min</b>   |
| Abbott ID Now SARS-CoV-2 <sup>22 31 47</sup>        | Symptomatic hospital patients | Meta-analysis: 73.0 (66.8 to 78.4)<br>TVG evaluation: 93.2 (84.3 to 97.5)                        | Meta-analysis: 99.7 (98.7 to 99.9) <sup>22</sup><br>TVG evaluation: 98.4 (96.5 to 99.3) | 13 min          |
| <b>RT-PCR</b>                                       |                               |                                                                                                  |                                                                                         |                 |
| DNANudge COVID-19 <sup>34 48</sup>                  | Symptomatic hospital patients | 82.1 (77.7 to 85.7)                                                                              | 99.1 (98.4 to 99.5)                                                                     | 90 min          |
| Horiba POCKIT SARS-CoV-2 <sup>49</sup>              | 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 <sup>35</sup>             | 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://www.finddx.org/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<sup>22</sup>

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<sup>34 35</sup> (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.<sup>36</sup>

### 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.<sup>37</sup> 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.<sup>25 38</sup> Lateral flow devices, arguably some of the simplest technologies, have demonstrated a 20% drop in sensitivity between experienced and inexperienced user groups.<sup>38</sup> 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.<sup>39</sup> 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<br>e.g. antigen tests                                                                                                                                                                     | High sensitivity and high specificity test<br>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.<br>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.<sup>40</sup> 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.<sup>41</sup>

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.<sup>42</sup> As such, multiplex testing will be an important priority

for the forthcoming winter, when other respiratory viruses with overlapping symptomatology 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.

**Twitter** Richard Body @richardbody

**Collaborators** CONDOR study steering committee members: Professor Richard Body, Professor Gail Hayward, Dr Joy Allen, Dr Julian Braybrook, Professor Peter Buckle, Professor Paul Dark, Dr Kerrie Davis, Miss Eloise Cook, Professor Adam Gordon, Mrs Anna Halstead, Professor Dan Lasserson, Dr Andrew Lewington, Dr Brian Nicholson, Professor Rafael Perera-Salazar, Professor John Simpson, Dr Philip Turner, Mr Graham Prestwich, Dr Charles Reynard, Mrs Beverley Riley, Mrs Valerie Tate and Professor Mark Wilcox.

**Contributors** CR and RB planned the manuscript. All authors contributed to the writing. All authors critically appraised the manuscript.

**Funding** This work is supported by the COVID-19 National Diagnostic Research and Evaluation Platform. COVID-19 National Diagnostic Research and evaluation(CONDOR) is grateful to receive funding from the National Institute for Health Research (NIHR), UK Research and Innovation, Asthma UK and the British Lung Foundation. CSP is supported by the National Institute for Health Research Greater Manchester Applied Research Collaboration. CR receives funding from the National Institute for Health Research, the Royal College of Emergency Medicine and Manchester University NHS Foundation Trust. JAA receives funding from the NIHR, Asthma UK and the British Lung Foundation for the CONDOR. JAA is also supported by the NIHR Newcastle In Vitro Diagnostics Co-operative. BS is supported by the NIHR Leeds In Vitro Diagnostics Co-operative (MIC). RB receives funding from the NIHR, Asthma UK and the British Lung Foundation for the CONDOR. KD receives funding from the NIHR, Asthma UK and the British Lung Foundation for the CONDOR.

**Disclaimer** The views expressed are those of the authors and not necessarily those of the funders, the NHS, the NIHR or the Department of Health and Social Care. In this practice review, we cover various technologies, we are not advocating for any given test and our coverage of commercially supplied tests is not intended to be exhaustive.

**Competing interests** RB has consulted for Siemens, Roche, Beckman, Singulex, LumiraDx and Abbott but not relating to COVID-19.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

#### ORCID iDs

Charles Reynard <http://orcid.org/0000-0002-7534-2668>

Joy A Allen <http://orcid.org/0000-0002-3222-0396>

Richard Body <http://orcid.org/0000-0001-9089-8130>

#### REFERENCES

- World Health Organization, World Health Organization. *Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19)*, 2020.
- Vanhems P, Saadatian-Elahi M, Chuzeville M, *et al*. Rapid nosocomial spread of SARS-CoV-2 in a French geriatric unit. *Infect Control Hosp Epidemiol* 2020;41:866–7.
- Kevadiya BD, Machhi J, Herskovitz J, *et al*. Diagnostics for SARS-CoV-2 infections. *Nat Mater* 2021;20:593–605.
- Erika P, Andrea V, Cillis MG, *et al*. Triage decision-making at the time of COVID-19 infection: the Piacenza strategy. *Intern Emerg Med* 2020;15:879–82.
- Wallace DW, Burleson SL, Heimann MA, *et al*. An adapted emergency department triage algorithm for the COVID-19 pandemic. *J Am Coll Emerg Physicians Open* 2020;1:1374–9.
- Graziadio S, Urwin SG, Cocco P, *et al*. Unmet clinical needs for COVID-19 tests in UK health and social care settings. *PLoS One* 2020;15:e0242125.
- Hicks T, Winter A, Green K, *et al*. Care pathway and prioritization of rapid testing for COVID-19 in UK hospitals: a qualitative evaluation. *BMC Health Serv Res* 2021;21:1–17.
- Douillet D, Saloux T, Ravon P, *et al*. Adaptation of ED design layout during the COVID-19 pandemic: a national cross-sectional survey. *Emerg Med J* 2021;38:789–93.
- Noble J, Degesys NF, Kwan E, *et al*. Emergency department preparation for COVID-19: accelerated care units. *Emerg Med J* 2020;37:402–6.
- Medicines & Healthcare products Regulatory Agency. Target product profile Point of Care SARS-CoV-2 Detection Tests [Internet], 2020. Available: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/895745/TPP\\_Point\\_of\\_Care\\_SARS-CoV-2\\_Detection\\_Tests.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/895745/TPP_Point_of_Care_SARS-CoV-2_Detection_Tests.pdf)
- World Health Organisation. Target product profiles for priority diagnostics to support response to the COVID-19 pandemic v.1.0 [Internet], 2020. Available: <https://www.who.int/publications/m/item/covid-19-target-product-profiles-for-priority-diagnostics-to-support-response-to-the-covid-19-pandemic-v.0.1>
- Cocco P, Ayaz-Shah A, Messenger MP, *et al*. Target product profiles for medical tests: a systematic review of current methods. *BMC Med* 2020;18:119.
- National Institute for Health and Care Excellence. Exploratory economic modelling of SARS-CoV-2 viral detection point of care tests and serology tests [Internet]. Available: <https://www.nice.org.uk/guidance/indevelopment/gid-dg10038/documents> [Accessed 14 Apr 2021].
- Stevenson M, Metry A, Messenger M. Modelling of hypothetical SARS-CoV-2 point-of-care tests on admission to hospital from A&E: rapid cost-effectiveness analysis. *Health Technol Assess* 2021;25:1.
- Stevenson M, Metry A, Messenger M. Modelling of hypothetical SARS-CoV-2 point of care tests for routine testing in residential care homes: rapid cost-effectiveness analysis. *Health Technol Assess* 2021;25:1–74.
- Cocco P, Messenger MP, Smith AF, *et al*. Integrating early economic evaluation into target product profile development for medical tests: advantages and potential applications. *Int J Technol Assess Health Care* 2021;37:e68.
- Kawasuji H, Takegoshi Y, Kaneda M, *et al*. Transmissibility of COVID-19 depends on the viral load around onset in adult and symptomatic patients. *PLoS One* 2020;15:e0243597.
- Fryer JF, Baylis SA, Gottlieb AL, *et al*. Development of working reference materials for clinical virology. *J Clin Virol* 2008;43:367–71.
- Zeichhardt H, Kammel M. Report on extra external quality assessment scheme group No. 340 virus genome Detection—SARS-CoV-2. INSTAND, Gesellschaft Zur Forderung Der Qualitätssicherung in medizinischen Laboratorien eV, Dusseldorf/Berlin 2020.
- The Centre for Evidence-Based Medicine. What tests could potentially be used for the screening, diagnosis and monitoring of COVID-19 and what are their advantages and disadvantages? [Internet]. Available: <https://www.cebm.net/covid-19/what-tests-could-potentially-be-used-for-the-screening-diagnosis-and-monitoring-of-covid-19-and-what-are-their-advantages-and-disadvantages/> [Accessed 14 Apr 2021].
- Vasudevan HN, Xu P, Servellita V, *et al*. Digital droplet PCR accurately quantifies SARS-CoV-2 viral load from crude lysate without nucleic acid purification. *Sci Rep* 2021;11:780.
- Dinnes J, Deeks JJ, Adriano A, *et al*. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. *Cochrane Database Syst Rev* 2020;8:CD013705.
- Peto T, Affron D, Afrough B, UK COVID-19 Lateral Flow Oversight Team. COVID-19: rapid antigen detection for SARS-CoV-2 by lateral flow assay: a national systematic evaluation of sensitivity and specificity for mass-testing. *EClinicalMedicine* 2021;36:100924.
- García-Fiñana M, Hughes DM, Cheyne CP, *et al*. Performance of the Innova SARS-CoV-2 antigen rapid lateral flow test in the Liverpool asymptomatic testing pilot: population based cohort study. *BMJ* 2021;374:n1637.
- Deeks JJ, Raffle AE. Lateral flow tests cannot rule out SARS-CoV-2 infection. *BMJ* 2020;371:m4787.
- Wolf A, Hulmes J, Hopkins S. Lateral flow device specificity in phase 4 (post marketing) surveillance [Internet]. Department of Health and Social Care, 2021. Available: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/968095/lateral-flow-device-specificity-in-phase-4.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/968095/lateral-flow-device-specificity-in-phase-4.pdf) [Accessed 14 Apr 2021].
- NHS England. Novel coronavirus (COVID-19) standard operating procedure Lateral flow device testing for emergency department patient pathways [Internet], 2020. Available: <https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/12/C0999-lateral-flow-testing-for-ed-patient-pathways-24-december-2020.pdf> [Accessed 14 Apr 2021].
- Dx L. LumiraDx SARS-CoV-2 Antigen Test - Instructions For Use [Internet]. Available: <https://www.lumiradx.com/assets/pdfs/covid-19-antigen-test/sars-cov-2-antigen-product-insert/sars-cov-2-ag-test-strip-product-insert-eua.pdf?v=6> [Accessed 26 May 2021].
- Drain PK, Ampajwala M, Chappel C, *et al*. A rapid, high-sensitivity SARS-CoV-2 nucleocapsid immunoassay to aid diagnosis of acute COVID-19 at the point of care: a clinical performance study. *Infect Dis Ther* 2021;10:753–61.
- Technical Validation Group, Department of Health and Social Care. Technical Validation for LumiraDx SARS-CoV-2 Ag test [Internet], 2021. Available: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/970905/TVG\\_Report\\_LumiraDx-v2.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/970905/TVG_Report_LumiraDx-v2.pdf)
- Technical Validation Group, Department of Health and Social Care. Technical Validation of Abbott ID Now [Internet], 2021. Available: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/951021/technical-validation-report\\_Abbot\\_ID\\_Now.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/951021/technical-validation-report_Abbot_ID_Now.pdf)
- Technical Validation Group, Department of Health and Social Care. Rapid evaluation of OptiGene RT-LAMP assay (direct and RNA formats) [Internet], 2020. Available: [https://www.gov.uk/government/publications/rapid-evaluation-of-optigene-rt-lamp-assay-direct-and-rna-formats](https://www.gov.uk/government/publications/rapid-evaluation-of-optigene-rt-lamp-assay-direct-and-rna-formats/rapid-evaluation-of-optigene-rt-lamp-assay-direct-and-rna-formats) [Accessed 15 Jun 2020].
- Optigene Limited. Optigene COVID-19 RNA RT-LAMP kit instructions for use [Internet], 2021. Available: [http://www.optigene.co.uk/wp-content/uploads/2021/06/IFU\\_RNA\\_v1.4.pdf](http://www.optigene.co.uk/wp-content/uploads/2021/06/IFU_RNA_v1.4.pdf) [Accessed 15 Jun 2021].
- Technical Validation Group, Department of Health and Social Care. Technical validation report for DNANudge [Internet], 2021. Available: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/978107/TVG\\_Report-DNANudge\\_1304.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/978107/TVG_Report-DNANudge_1304.pdf) [Accessed 15 Jun 2021].
- Technical Validation Group, Department of Health and Social Care. Technical Validation for the Real World, SAMBA II SARS-CoV-2 Test (REF 8500-12) [Internet], 2020. Available: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/941767/technical-validation-report-SAMBA-II.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/941767/technical-validation-report-SAMBA-II.pdf) [Accessed 15 Jun 2021].
- CONDOR Data Dashboard. CONDOR - COVID19 National Diagnostic Research and Evaluation Platform Study. Available: <https://www.condor-platform.org/condor-activity-report?ref=image> [Accessed 15 Sep 2021].
- Usher-Smith JA, Sharp SJ, Griffin SJ. The spectrum effect in tests for risk prediction, screening, and diagnosis. *BMJ* 2016;353:i1319.
- Peto T, UK COVID-19 Lateral Flow Oversight Team. COVID-19: rapid antigen detection for SARS-CoV-2 by lateral flow assay: a national systematic evaluation of sensitivity and specificity for mass-testing. *EClinicalMedicine* 2021;36:100924.
- World Health Organization. *Laboratory biosafety guidance related to coronavirus disease (COVID-19): interim guidance*. World Health Organization, 2020.
- Mina MJ, Peto TE, García-Fiñana M, *et al*. Clarifying the evidence on SARS-CoV-2 antigen rapid tests in public health responses to COVID-19. *Lancet* 2021;397:1425–7.
- Fearon E, Fyles M. On the use of LFA tests in contact tracing: preliminary findings. :8.
- Exclusive: Government alert over surge in respiratory virus affecting babies and toddlers | News | Health Service Journal [Internet]. Available: <https://www.hsj.co.uk/public-health/exclusive-government-alert-over-surge-in-respiratory-virus-affecting-babies-and-toddlers/7030061.article> [Accessed 23 Jun 2021].
- Abbott. Instructions for use - Panbio [Internet]. Available: <https://dam.abbott.com/en-gb/panbio/120007883-v1-Panbio-COVID-19-Ag-Nasal-AsymptomaticSe.pdf> [Accessed 15 Sep 2021].

- 44 Frediani JK, Levy JM, Rao A, *et al.* Multidisciplinary assessment of the Abbott BinaxNOW SARS-CoV-2 point-of-care antigen test in the context of emerging viral variants and self-administration. *Sci Rep* 2021;11:14604.
- 45 Abbott. Instructions for use - BinaxNOW [Internet]. Available: [fda.gov/media/141570/download](https://www.fda.gov/media/141570/download) [Accessed 15 Sep 2021].
- 46 Innova. Instructions for use - Innova COVID-19 Antigen Detection Lateral Flow Device 2021.
- 47 Abbott. Instructions for Use - ID NOW COVID-19 [Internet]. Available: <https://www.fda.gov/media/136525/download> [Accessed 15 Sep 2021].
- 48 dnanudge. Instructions for use - CovidNudge [Internet]. Available: <https://www.dnanudge.com/v6/uploads/files/CovidNudge-IFU.pdf> [Accessed 15 Sep 2021].
- 49 Technical Validation Group. Validation Report for Horiba POCkit [Internet]. Department of Health and Social Care, 2020. Available: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/941770/technical-validation-report-Horiba-POCKIT.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/941770/technical-validation-report-Horiba-POCKIT.pdf) [Accessed 15 Sep 2021].