Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Rapid health technology assessment of alternative diagnostic testing approaches for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

17 April 2020

Safer Better Care

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HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children and Youth Affairs, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
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- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
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- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

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Conflicts of interest

None reported.

List of abbreviations used in this report

ARI	acute respiratory infection
ARTG	Australian Register of Therapeutic Goods
CE	Conformité Européene
CDC	Centre for Disease Prevention and Control
cDNA	complementary deoxyribonucleic acid
COVID-19	Coronavirus disease 2019
CRISPR	clustered regularly interspaced short palindromic repeats
CT	computed tomography
CTS	common technical specifications
DNA	deoxyribonucleic acid
DTA	diagnostic test accuracy
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ELISA	enzyme-linked immunosorbent assays
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FSCA	field safety corrective actions
HIQA	Health Information and Quality Authority
HIV	human immunodeficiency virus
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
HTA	health technology assessment
HZI	Helmholtz Centre for Infection Research
ICU	intensive care unit
IFA	immunofluorescence assays
IgG	immunoglobulin G
IgM	immunoglobulin M

ILI	influenza-like illness
IVD	in vitro diagnostics
IVDR	In Vitro Diagnostic Regulation
JRC	Joint Research Centre
MERS	Middle East Respiratory Syndrome
MHRA	Medicines and Healthcare products Regulatory Authority
NAAT	nucleic acid amplification technology
NPHET	National Public Health Emergency Team
RNA	ribonucleic acid
RT-LAMP	reverse transcription loop-mediated isothermal amplification
RT-PCR	reverse transcription polymerase chain reaction
SARI	severe acute respiratory infections
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SHERLOCK	Specific High Sensitivity Enzymatic Reporter UnLOCKing
TGA	Therapeutic Goods Administration
WHO	World Health Organization

Executive summary

The Health Information and Quality Authority (HIQA) was requested to undertake a rapid health technology assessment (HTA) of alternative diagnostic testing methods for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to inform the work of the National Public Health Emergency Team (NPHET) in their response to the COVID-19 (coronavirus disease 2019) pandemic. The World Health Organization (WHO) has identified that diagnostic testing for SARS-CoV-2 infection is critical to tracking the viral spread, understanding epidemiology, informing case management, and reducing transmission.

The assessment was undertaken as a rapid HTA within very restricted timelines and in the context of an evolving global pandemic of a new pathogen in humans. It therefore differs from a standard HTA in its scope and the approaches adopted to synthesising the available evidence.

At the request of NPHET, HIQA investigated the potential usefulness of alternative diagnostic tests for the detection of SARS-CoV-2, whether any of the tests that are commercially available are being used internationally, and identified when the tests could be deployed in the clinical pathway.

Potential alternative diagnostic approaches

Diagnostic tests for SARS-CoV-2 can broadly be grouped into two categories, those aimed at:

- pathogen (virus) detection (acute infection)
- detection of immune response to the pathogen (past exposure).

Reverse transcription polymerase chain reaction (RT-PCR) facilitates direct detection of SARS-CoV-2 RNA. It is characterised by high sensitivity and specificity, and is regarded as the gold standard for clinical diagnostics. The initial identification of the SARS-CoV-2 virus was based on non-commercial RT-PCR laboratory protocols which were published on the World Health Organization (WHO) website. The testing protocols include multiple steps involving manual manipulation and take six to seven hours to complete. However, RT-PCR is not a new technology; it is widely used in specialised diagnostic virology laboratories. Therefore, companies have developed and commercialised RT-PCR test kits, many of which work off existing platforms already deployed in Irish hospital and diagnostic virology laboratories.

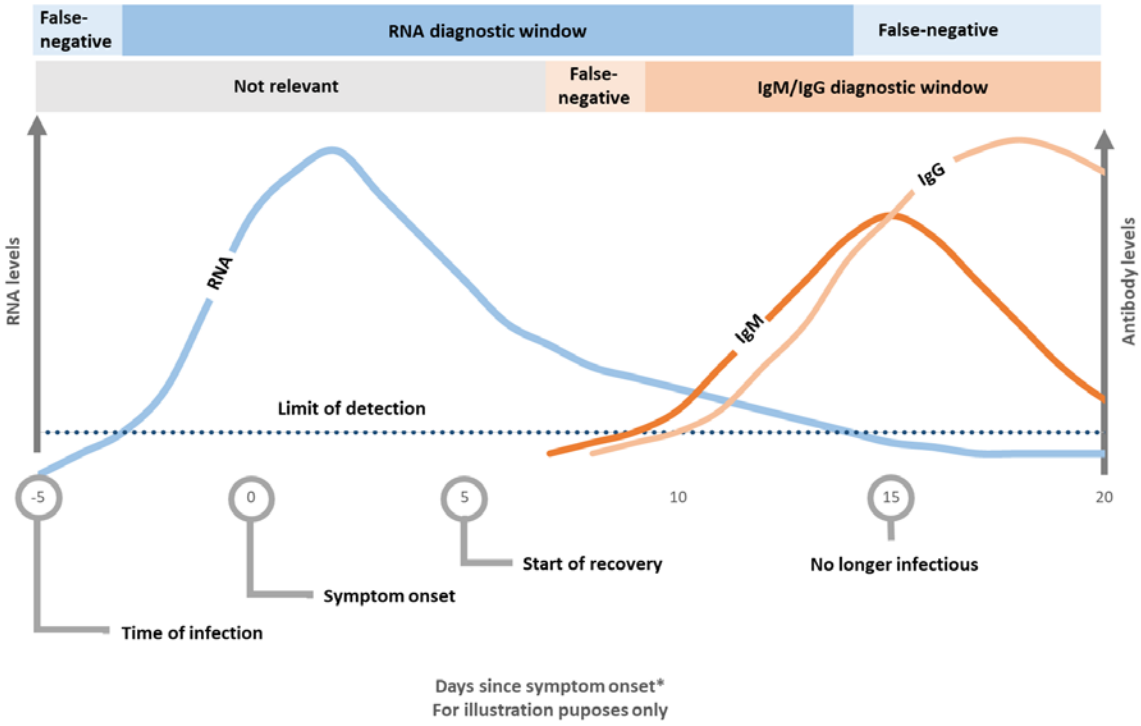
Potential alternative or additional approaches to RT-PCR considered in this assessment include: serological testing (for antibodies and antigens); microarray or microfluidic lab-on-chip technologies; CRISPR to isolate gene segments; and full

genetic sequencing. Rapid tests involving in-vitro diagnostics (IVDs) which have the potential to be used at or near the point of care (near-patient testing) were also considered.

Operational utility

Pathogen detection tests (such as RT-PCR) and tests to detect an immune response to the virus (development of SARS-CoV-2-specific antibodies) should not be considered competing alternatives. Both testing approaches are clinically relevant, but must be deployed at different time points during the clinical course of infection taking consideration of their relevant diagnostic windows (Figure ES1).

Figure ES1: Diagnostic windows for the detection of acute SARS-CoV-2 infection (viral RNA) and the immune response (anti-SARS-CoV-2 IgM and IgG) indicating past exposure to SARS-CoV-2



Note: *While the sequence of events is well understood, the exact timeline is based on early evidence summaries and is subject to considerable uncertainty.

Case finding – detection of acute infection

RT-PCR is the 'gold standard' recommended for use by the WHO and ECDC for the diagnosis of COVID-19 cases during the acute phase of infection. It is indicated for the detection of SARS-CoV-2 RNA early in the clinical course of infection. False negative results can occur if testing takes place in the initial incubation period following infection. The minimum duration from infection to a positive test remains uncertain. Using RT-PCR, SARS-CoV-2 viral RNA can be detected one-to-two days prior to symptom onset in upper respiratory tract samples (Figure ES1). Based on

limited early data, viral load peaks around the time of symptom onset, with viral RNA becoming undetectable (from upper respiratory tract specimens) approximately two weeks following symptom onset. The diagnostic window for using RT-PCR to detect acute infection with SARS-CoV-2 therefore ranges from approximately three days following exposure to the virus until two weeks following symptom onset (Figure ES1).

Antigen detection tests, including rapid antigen tests, could be used to facilitate early diagnosis of acute infection with SARS-CoV-2. In general, available antigen detection tests, although associated with operational advantages in terms of ease-of-use and turnaround time, are less sensitive when compared with RT-PCR. A highly sensitive test is necessary to prevent false negative results and the risk of potential virus transmission. In the absence of independent validation, the WHO has advised against the use of rapid diagnostic tests based on antigen detection in any setting (except research settings), including for decision-making, until evidence supporting their use for specific indications is available. Consideration may, in future, be given to the use of rapid antigen tests as triage tests to rapidly identify patients who are considered very likely to have COVID-19 based on clinical symptoms and epidemiological risk factors, thereby reducing the need for molecular (RT-PCR) confirmatory testing.

Identification of prior infection

Direct viral detection methods such as RT-PCR and antigen detection tests cannot be used to identify past exposure to SARS-CoV-2. To identify those who have been exposed to SARS-CoV-2, tests that detect antibodies (IgM and IgG) produced by the body in response to SARS-CoV-2 infection can be used. Antibodies are typically detectable 7-to-14 days (a week to a fortnight) after the onset of symptoms. Therefore, antibody detection tests are not useful for early case finding.

As SARS-CoV-2 is a new pathogen in humans, little is known regarding the adequacy of the immune response or the duration of immunity following seroconversion (development of SARS-CoV-2-specific antibodies). Therefore, it is not known if reinfection can occur, although there is no reason to assume it cannot. In addition, as with the influenza virus, there is potential for antigenic drift, and thus the potential that any immunity following infection would be limited to the initial strain of the virus.

A highly specific test is necessary to prevent false positive results, whereby individuals are incorrectly classified as potentially being immune to SARS-CoV-2, when they are still at risk of contracting the infection. Similar to the rapid antigen tests, the WHO has advised against the use of rapid antibody tests in any setting

(except research settings), including for decision-making, until evidence supporting their use for specific indications is available.

The operational utility of antibody detection tests can be considered in the context of three potential scenarios:

- **Patient-level testing to inform clinical management.** For example, in addition to any existing requirements to confirm disappearance of viral RNA, a decision to de-escalate care for patients hospitalised with COVID-19 could be informed by additional antibody testing to detect the presence of IgG antibody specific to SARS-CoV-2.

- **Cohort testing to inform staff deployment.** For example, proposed 'immunity passports' to enable staff with immunity to the virus to return to work, or in the context of healthcare workers, preferential deployment of staff with acquired immunity to high-risk areas on the basis that they would not be considered at risk of contracting or spreading the disease.

- **Population level seroepidemiological studies to inform public health strategies.** Surveillance studies based on detection of antibodies specific to SARS-CoV-2 could be a useful public health tool to assess overall infection and immunity rates in the population (for example, those immune due to mild, asymptomatic or recovered infection) and so inform the relaxation of public health measures. However, issues in relation to cross-reactivity to other coronaviruses (that is, risk of false-positives) and persistence of immunity require clarification. Surveillance studies are planned or underway in a number of countries including Germany, France, and the UK.

The level(s) at which such antibody detection tests might be deployed has extremely important implications for both the administration and reporting of tests as well as the overall governance of any testing strategy. This is particularly the case for testing to inform staff redeployment given the uncertainty around the effectiveness and durability of the antibody response, and the potential for re-infection with the same or a different antigenic strain of the SARS-CoV-2 virus.

The use of population-level antibody detection studies to inform a public health response is well documented in the context of other viral respiratory pathogens. Such studies are resource intensive. Interpretation of the findings is critically dependent on a wide range of factors including the demographics of the population tested, the specificity of the test used and issues relating to the sample type and handling. Any decision to implement population-level testing should therefore only be undertaken in the context of a well-designed research study with governance and controls usual to such studies.

Current international practice

A brief scoping review was undertaken to identify the diagnostic approaches being recommended internationally. Included in the review were international agencies and a limited number of European and non-European countries.

The WHO, ECDC, and the CDC in the US recommend using laboratory-based nucleic acid amplification (molecular) tests (manual or automated), such as RT-PCR to detect the SARS-CoV-2 RNA (as of 14 April 2020). The same molecular test has been recommended for use to detect acute infection with SARS-CoV-2 in Ireland and the UK, among other countries.

Microfluidic lab-on-chip technologies and genetic sequencing do not appear to be used at a national level in any country for the detection of COVID-19. Although not yet CE-marked, a microarray respiratory panel incorporating SARS-CoV-2 is reported to be in use in the UK. Genomic surveillance will be important to monitor the virus for the appearance of mutations and to identify stable targets for nucleic acid based detection methods. Viral genome sequences could also inform the development of treatments and vaccines. In the UK, the COVID-19 Genomics UK Consortium, comprising the National Health Service (NHS), Public Health England, UK Research and Innovation (UKRI), and Wellcome has been launched to track viral spread and evolution via genome sequencing of COVID-19 samples.

The WHO and ECDC recommend that a serum sample for serology (that is, antibody testing) should be collected and stored during the acute phase of illness (that is, after symptom onset), with a second serum sample collected two-to-four weeks later, during the convalescent phase. Having a baseline sample allows confirmation that seroconversion has occurred. It can also facilitate retrospective case definition in individuals who did not have timely access to RT-PCR to confirm acute infection.

While not implemented at a national level, there is anecdotal evidence that rapid antibody tests have been deployed in a number of healthcare settings (Veneto and Emilia-Romagna regions in Italy; Mount Sinai Hospital and Mayo Clinic in the US).

Availability of diagnostic tests approved for use internationally

In Europe, tests for COVID-19 (SARA-CoV-2) which are CE marked in accordance with the *In Vitro* Diagnostic Medical Devices Directive (IVDD; 98/79/EC) may be placed on the market. Under this Directive, manufacturers of tests for COVID-19 (SARS-CoV-2) are required to specify device performance characteristics and self-declare conformity with the safety and performance characteristics outlined in the Directive. Self-tests for COVID-19 (SARS-CoV-2) require independent assessment by a Notified Body to ensure the requirements of the IVD Directive are met. New

technologies for the diagnosis of COVID-19 are rapidly emerging and regulatory agencies are responding quickly to this emerging pathogen. This has included the creation of pathways to accelerated regulatory approval to meet worldwide demand for diagnostic testing (for example FDA's Emergency Use Authorization). In Europe, due to the scale of the pandemic, some regulatory authorities are facilitating the placement on the market of non-CE marked IVDs deemed critical for COVID-19 diagnosis through national derogations.

In Ireland, the Health Products Regulatory Authority (HPRA) is the Competent Authority (CA) for medical devices and IVDs, and monitors the safety of medical devices and IVDs after they have been placed on the market. The HPRA has developed a regulatory derogation process for the urgent assessment of applications to facilitate the use of critical non-CE marked medical devices and IVDs in the context of the COVID-19 emergency in Ireland.

A list of test devices for detection of SARS-CoV-2 was compiled through a review of data from a variety of grey literature sources including online repositories (such as the non-governmental organisation, FIND).

Performance of commercialised diagnostic tests

While a systematic review of the literature is routinely used in HTAs to assess diagnostic test accuracy, this approach was not adopted in this rapid assessment as such a review was considered premature at this point. SARS-CoV-2 is a novel pathogen in humans first detected in December 2019. Literature published in the first four months of this year are primarily in the form of case reports and case series. These would require confirmation using larger more robust study designs. It is also noted that at the time this assessment was being undertaken, the majority of the publications had not undergone peer-review, therefore the study findings should be interpreted with caution.

In the absence of a centralised list of verified CE-marked tests, a review of grey literature sources including online repositories (such as the non-governmental organisation, FIND) was undertaken to identify IVD tests for COVID-19 claiming CE-marking. Due to time constraints, the claimed CE-marking was not verified with relevant authorities. The performance data are limited to manufacturer-reported characteristics, so may be subject to bias. The purpose of this review is to illustrate the range of IVDs commercialised for COVID-19.

A large number of RT-PCR test kits were identified. The initial RT-PCR testing protocols approved and validated for SARS-Co-V2 detection include multiple steps involving manual manipulation and take six to seven hours to complete. Newly-developed kits incorporate existing technological advances and can be used in

platforms with a higher degree of automation, requiring less manual manipulation, less reagent and that are amenable to batch testing, thereby facilitating quicker turnaround time and a higher throughput of tests.

Advantages of test kits suitable for use on existing platforms include the fact that the platforms are already deployed in a number of the hospital laboratories, so there is a level of multidisciplinary experience and confidence in their use.

Forty-two laboratory-based RT-PCR tests were identified, 17 of which were identified as being CE-marked by the manufacturer. Of the 17 devices, five manufacturers reported diagnostic test accuracy results. Clinical sensitivity ranged from 89% to 100%, and clinical specificity ranged from 98% to 100%.

Given the need for specialised equipment and reagents, technically skilled staff and potential long turnaround times with RT-PCR, alternative diagnostic methods with comparable accuracy and reduced operational requirements are needed. There is evidence to suggest that nucleic acid detection-based methods such as CRISPR and RT-LAMP may have comparable diagnostic test accuracy to RT-PCR, and may have operational advantages in terms of ease-of-use and turnaround time. Many of these devices are still in the development stage. In our initial review, commercially available CE-marked tests using these methodologies were not identified.

Rapid antigen and antibody tests

Although an increasing number of alternative diagnostic tests are being developed and commercialised, there is considerable uncertainty regarding the clinical performance of these tests, in particular rapid SARS-CoV-2 antigen detection tests and rapid antibody tests.

Using publicly available information from the non-governmental organisation, FIND, the ECDC reported that ten rapid antigen IVDs conform with the relevant EU legislation, Directive 98/79/EC on in-vitro diagnostic medical devices (IVDs), and may be available for use internationally. However, they noted that they may be targeted to third-country markets and may not be available for purchase in the EU. According to authorities in 18 European countries, three rapid antigen tests have been reported as CE-marked, as of 26 March. However, no manufacturer data on the accuracy of these tests was identified. No data to support their independent validation has been published.

The ECDC reported that over 60 rapid SARS-CoV-2 antibody tests have been CE marked to date, and many more continue to be placed on the market. As noted, CE-marking of tests for COVID-19 (SARS-CoV-2), with the exception of self-tests, is based on self-declaration. In an initial review of tests claiming CE-marking, clinical

sensitivity and specificity was reported by eight manufacturers. Across all of these data (n=8), clinical sensitivity ranged from 85% to 100%, and clinical specificity ranged from 96% to 100%. However, these ranges should be interpreted with caution given that the reference standard used for comparison was not always reported by manufacturers. As yet, none of the rapid antibody tests have been independently validated, and, to date, there are no CE-marked antibody tests for self-testing available.

Pre-analytical vulnerabilities, independent clinical validation and quality assurance

The pre-analytical phase can be a major source of errors in diagnostic testing. To mitigate such risks, training and quality assurance procedures are required to ensure that test samples are appropriately identified and reported (right result, right patient), and to ensure adequate procedures for correct specimen (for example, swab) collection, handling, transport, and storage.

Performance of both laboratory-based tests and rapid tests performed outside the laboratory (near-patient tests) may differ to that reported by manufacturers for the purposes of CE-marking. Prior to their introduction as standalone diagnostic tests, independent clinical validation of the diagnostic performance compared with a reference standard is considered best practice.

On the 16 April 2020, the European Commission published a working document that provides additional guidance to the legally obligatory requirements defined in the IVDR. The guidelines highlight the distinction between analytical performance (usually evaluated based on a number of well-defined laboratory samples and extreme patient samples) and diagnostic test accuracy which should be performed in clinical studies using head-to-comparison between the test under assessment and the reference test in the target population intended to be tested. Based on the principles of good analytical (testing) practice, these guidelines include performance criteria for RT-PCR, antigen-based and antibody-based tests. The current absence of control samples and reference materials are noted as a particular challenge to establishing the diagnostic test accuracy of antigen and antibody tests.

Commercialised, CE-marked, rapid tests are being assessed by WHO referral laboratories and in clinical validation studies funded by the European Commission and EU member states. The results of the validation studies will be published as soon as they are available to inform decision-making regarding their potential use. At that point, the WHO and ECDC have noted that they will update their guidance on testing using these validated diagnostic testing approaches, which may be used in laboratories or near the point of care. Until these studies have been validated, the

WHO strongly advises against the use of rapid tests, in particular antigen detection and host antibody detection tests, in any setting other than research.

In addition to independent external validation studies, additional verification studies are considered best practice prior to test deployment. This is to ensure adequate performance of the tests in the context in which they are being used. For RT-PCR test kits, clinical validation of the diagnostic performance of the test kit should be compared with an existing validated protocol for the gold-standard, but may be conducted on the basis of a truncated validation run involving fewer samples, with risk mitigated by enhanced surveillance of test performance, given the current requirements for rapid deployment.

While adequate test accuracy and precision may be achieved under idealised circumstances in the laboratory, these may be negatively impacted when used at the point of care. Appropriate staff training and use of robust standardised operating procedures may be required to moderate these sources of error.

In accordance with existing Irish guidelines for the safe and effective management and use of near-patient (point-of-care) diagnostic tests, such testing should be performed in the context of an ongoing quality assurance programme to ensure adequate performance of the tests in the context in which they are being used and provide confidence in the test results for both the diagnosing physician and the patient. Consideration should also be given to a requirement that all testing should be ISO-accreditable, including meeting requirements in relation to internal quality control, quality assurance and the recording of training and test results.

Conclusions

This assessment was undertaken as a rapid HTA within very restricted timelines and in the context of an evolving global pandemic of a new pathogen in humans. It therefore differs from a standard HTA in its scope and the approaches adopted to synthesising the available evidence. Evidence to support the analytical performance of diagnostic tests for SARS-CoV-2 will continue to emerge. Evidence will also emerge to support the clinical effectiveness and safety of different testing strategies to inform patient care and the public health response to COVID-19. Revisions to any national testing strategy may be required as the evidence evolves. In time, a full HTA that takes consideration of the cost-effectiveness, resource considerations and budget impact of alternative testing strategies may be required to ensure the best outcomes for the resources available.

Bearing in mind the caveats of the approach adopted, and arising from the findings of this report, the following conclusions can be drawn:

- Diagnostic tests for SARS-CoV-2 can be broadly grouped into two categories: those aimed at detecting the virus and those that detect the body's immune response to the infection (past exposure to the virus). These should not be considered competing alternatives; both testing approaches are clinically relevant at different time points during the clinical course of infection.
- The ability of any diagnostic test to achieve an acceptable clinical performance is contingent on it being performed within the appropriate timeframe for the condition in question (right test, right time, right person), with due consideration of the principles of good pre-analytical and analytical testing practice.
- Real-time PCR is the preferred method to detect SARS-CoV-2 RNA and to confirm acute infection early in the clinical course of COVID-19 disease. To increase diagnostic testing capacity, efforts are underway to develop enhanced molecular methods with reduced turnaround times and instrumentation requirements and higher throughput.
- Antigen detection tests could be used to supplement current laboratory-based real-time RT-PCR case detection. However, analytical and clinical validation of these tests is needed to inform their safe and effective use in clinical decision-making.
- Contingent on the availability of accurate, validated tests, antibody tests could be used later in the clinical course of infection or following recovery to identify those who have been exposed to SARS-CoV-2. While the use of antibody tests to provide 'immunity passports' has been proposed in the literature, little is known about the adequacy of the immune response or the duration of immunity, and so it is not known if reinfection can occur. The primary role of antibody tests is likely to be as part of well-constructed seroprevalence studies to model the course of the pandemic and inform the public health response.
- Work is currently underway to validate the analytical performance of the different diagnostic tests. Prior to their introduction as standalone tests, clinical validation studies are also required to confirm that test performance can be replicated in the context in which the test is being used. All testing should be undertaken in the context of an ongoing quality assurance programme to provide confidence in the test results for both the physician and the patient.
- A cohesive national strategy is needed to ensure the right tests are undertaken in the right people at the right time for the right purpose. This is necessary to

ensure appropriate governance of SARS-CoV-2 testing and should include clear criteria for the administration and reporting of tests. Planning now to support delivery of the strategy will facilitate rapid deployment of tests that meet the requisite standards once available and validated for use.

1. Background

The Health Information and Quality Authority (HIQA) has been asked to summarise the best available evidence regarding the diagnostic testing methods for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to inform the work of the National Public Health Emergency Team (NPHET) in their response to COVID-19 (Coronavirus Disease 2019). The World Health Organization (WHO) has identified that diagnostic testing for SARS-CoV-2 infection is critical to tracking spread of the virus, understanding epidemiology, informing case management, and reducing transmission.

The assessment was undertaken as a rapid assessment within very restricted timelines and in the context of a global pandemic involving a new pathogen. It therefore differs from a standard health technology assessment (HTA) in its scope and the approaches adopted to synthesising the available evidence.

The request noted that most of the available diagnostics have focused on packaging the appropriate reagents, genetic primers and probes for using reverse transcription polymerase chain reaction (RT-PCR) to amplify genetic material for detection of SARS-CoV-2 RNA. In this context, the following questions were posed which inform the scope of the report:

1. What are the potential alternative approaches to RT-PCR, including:
   - serological testing
   - microarray or microfluidic lab-on-chip technologies
   - CRISPR to isolate gene segments for diagnostics
   - full genetic sequencing
   - rapid tests (suitable for near-patient testing)?
2. What alternative diagnostic testing approaches are currently being used internationally?
3. What is the rationale for, and operational utility of, serological tests (or other approaches) in the 'pre-symptomatic-symptomatic-full resolution' clinical pathway (for example, rapid diagnostics, seroprevalence studies)?
4. What alternative diagnostic tests have been CE-marked for use in Europe and or approved or authorised for use by the US Food and Drug Administration, among other international regulatory authorities?
5. What are the performance characteristics of alternative diagnostic testing approaches, including:
   - sensitivity and specificity
   - turnaround time
   - deployment approaches
   - organisational and or infrastructural requirements?

These questions are addressed in sequence in Section 2 to Section 6. A general discussion of key issues likely to be of relevance to decision making by the NPHET in relation to deployment of the alternative testing approaches is provided in Section 7.

Work on this assessment was informed by detailed discussions and feedback from expert stakeholders in this area, specifically:

- National Clinical Lead for the HSE's National Clinical Programme for Pathology
- National Clinical Lead for the HSE's Antimicrobial Resistance and Infection Control Team
- Director of the National Virus Reference Laboratory
- Health Products Regulatory Authority (HPRA) which is designated as the Competent Authority (CA) for medical devices and in vitro diagnostic medical devices (IVDs) in Ireland.

2. Description of the technology

Key points

- Real-time RT-PCR is the current gold standard for the detection of SARS-CoV-2 RNA during the acute stage of COVID-19 disease.
- RT-PCR has many limitations including the need for specialised equipment and reagents, technically skilled staff and long turnaround times.
- Alternative isothermal nucleic acid amplification methods (for example, RT-LAMP) may have advantages over real-time RT-PCR in terms of ease-of-use and turnaround time.
- Antigen detection tests detect the presence of viral proteins in clinical samples. While generally less accurate than real-time RT-PCR, they have a faster turnaround time, and are easier to operate.
- Antibody tests detect antibodies (IgM and IgG) produced by the immune system in response to infection with SARS-CoV-2.
- Rapid tests have been developed for use in near-patient or resource-constrained settings to accelerate clinical decision-making and expand testing capacity.
- Surveillance using genetic sequencing will be important to identify any mutations in the virus that may reduce the sensitivity of diagnostic tests.

2.1. Coronaviruses

Coronaviruses are a large family of viruses that circulate among animals including camels, cats and bats. They can be spread from animals to humans. Coronaviruses cause illness in humans ranging from the common cold to more severe respiratory (lung) diseases.[1] Symptoms can include cough, shortness of breath, difficulty breathing and fever. In more severe cases, pneumonia, severe acute respiratory syndrome, kidney failure and death can occur.[2]

To date, seven coronaviruses have been shown to infect humans. Common human coronaviruses including *Alphacoronavirus* HCoV-229E, *Betacoronavirus* HCoV-OC43, and HCoV-HKU1 and *Alphacoronavirus* HCoV-NL63 are generally associated with mild clinical symptoms. Additional zoonotic coronaviruses (SARS-CoV and Middle

East respiratory syndrome coronavirus [MERS-CoV]) have emerged and have been associated with more severe complications.(2)

In December 2019, a virus that had not previously been seen in humans was identified in Wuhan, China. SARS-CoV-2 (previously known as 2019 Novel coronavirus [2019-nCov]) shares a high degree of sequence similarity with SARS-CoV.(3) Therefore, diagnostic testing approaches must be aimed at target gene sequences or their resultant proteins that are specific to SARS-CoV-2.

2.2. Diagnostic testing

The World Health Organization (WHO) recognises that there is no universal best practice approach to the management of COVID-19, and that good laboratory practices that produce consistently accurate results are key to assuring that laboratory testing supports the public health response.(4) There is a need to provide guidance on the best available testing methodologies under different public health scenarios for identification of current or resolved cases to inform public health measures. Diagnostic testing for SARS-CoV-2 infection is critical to tracking the viral spread, understanding epidemiology, informing case management, and reducing transmission.(4)

Testing methods available for the detection of SARS-CoV-2 infection include those aimed at pathogen detection and those aimed at detecting the immune response to the pathogen.

Pathogen detection tests (discussed in section 2.3) include

- Molecular methods (discussed in section 2.3.1) to detect viral RNA including RT-PCR, isothermal RNA amplification methods and genetic sequencing.
- Antigen detection tests (discussed in section 2.3.2).
- Viral culture (section 2.3.3).
- Microarrays and microfluidic technologies (discussed in section 2.3.4) can be designed to detect a range of targets including viral RNA, antigens

Detection of the host immune response (discussed in section 2.4):

- Antibody tests.
- Microarrays and microfluidic technologies which can also be developed to detect antibodies.

Rapid tests (discussed in section 2.5) are in vitro diagnostic (IVD) medical devices which involve non-automated procedures and have been designed to give a fast result for near-patient (point-of-care) testing. These include pathogen detection tests and tests to detect the immune response.

A summary of the testing methods available is provided in Table 2.1 at end of this section along with a brief description of the suggested advantages, limitations and potential applications of these technologies.

2.3. Pathogen detection tests

2.3.1. Molecular methods

Reverse-transcription polymerase chain reaction (RT-PCR)

Reverse transcription polymerase chain reaction (RT-PCR) is a genetic amplification technique that measures RNA expression levels. In RT-PCR, complementary DNA (cDNA) is made by reverse transcription of RNA templates with the enzyme reverse transcriptase. This technique can be used to:

- qualitatively study gene expression
- relatively or absolutely quantitate RNA levels (real-time RT-PCR).[5]

RT-PCR facilitates direct detection of SARS-CoV-2 genetic material in various patient specimens such as blood, stool, respiratory secretions or body tissues and can be used for early diagnosis. Real-time RT-PCR (that is, the amplification of target RNA is monitored as it occurs) is characterised by high sensitivity and specificity, and is regarded as the gold standard for clinical diagnostics.[6, 7]

The first RT-PCR tests for detecting SARS-CoV-2 were designed and distributed in January 2020 by the World Health Organization (WHO). Protocols for RT-PCR testing have been developed by other countries (including Germany, Hong Kong, China, Thailand, Japan and France), some of which have been made available on the WHO website.[4] The protocol for testing in the US is available on the Centre for Disease Control and Prevention's (CDC) site.[8]

These RT-PCR assays target one or more of the following genes of SARS-CoV-2:

- open reading frame1a/b (ORF1a/b)
- ORF1b-nuclear shuttle protein14 (ORF1b – nsp14)
- RNA-dependent RNA polymerase (RdRp)
- spike (S)

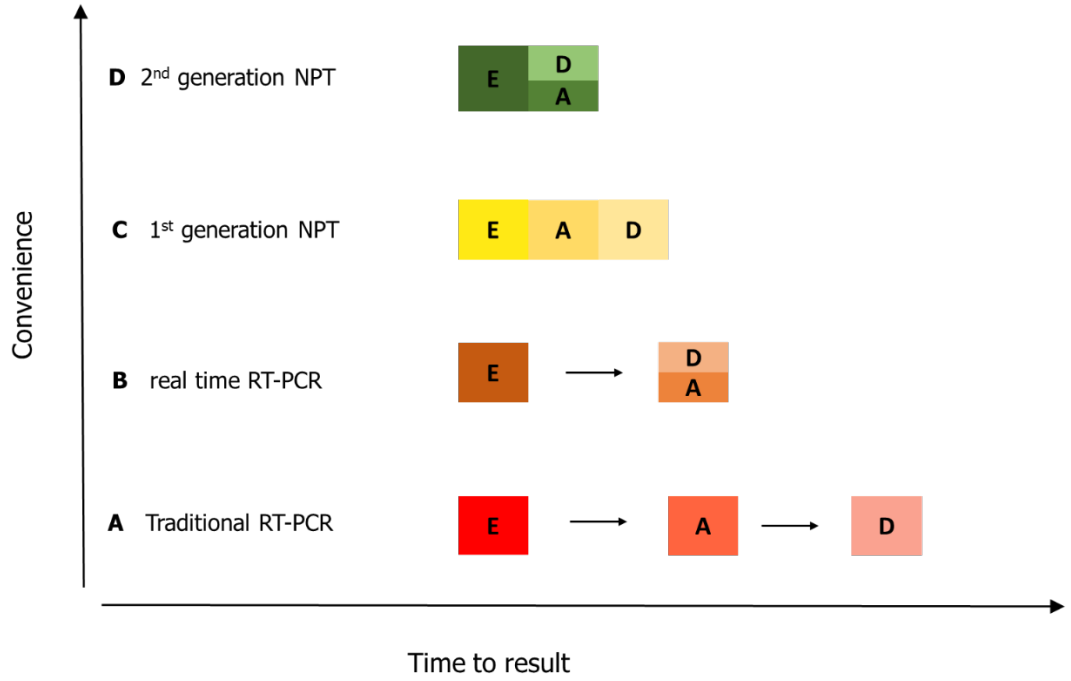
- envelope (E)
- nucleocapsid (N) genes.[9]

Despite its widespread use, RT-PCR has many limitations including the requirement for highly skilled staff and specialised laboratory instrumentation for sample processing, as well as long reaction times. These disadvantages limit its practical application, and thus can delay the rapid identification and isolation of individuals with COVID-19, thereby potentially contributing to onward disease transmission.

Technological advances and variations of RT-PCR

The initial testing protocols include multiple steps involving manual manipulation and take six to seven hours to complete. However, RT-PCR is not a new technology; it is widely used in specialised laboratories for viral testing. Companies have developed and commercialised RT-PCR test kits, many of which work off existing platforms already deployed in hospital and testing laboratories. These kits incorporate existing technological advances that increase the convenience of testing and reduce test processing times (see Figure 2.1). Use of rapid RT-PCR kits should leverage existing laboratory resources to optimise the expansion of testing.

Figure 2.1: Technological advances leading to improved efficiency of nucleic acid amplification-based testing procedures



Key: A – Amplification; D – Detection; E – Extraction; NPT – near-patient test; RT-PCR – reverse transcription polymerase chain reaction. Figure adapted from Loeffelholz et al.[10]

Real-time RT-PCR combines amplification and detection into a single step thereby monitoring the generation of PCR products as it occurs (Figure 1, B and D). Real-time RT-PCR is favoured for viral diagnostics due to the reduced turnaround time.

In the one-step real-time RT-PCR method, reverse-transcription and PCR are carried out in the same tube.[11] One-step protocols are in development as another potential strategy to increase the convenience of RT-PCR. Two-step methods involve the creation of cDNA in a separate reverse-transcription reaction, followed by the addition of this cDNA to the PCR reaction. While one-step methods increase ease of use, they are usually less sensitive as it is impossible to optimise the two reactions separately. One-step protocols are best suited to laboratories carrying out screening of multiple samples for repetitive tests, or high-throughput screening.[12]

Multiplex RT-PCR is a variation of RT-PCR in which multiple targets are amplified simultaneously, facilitating the detection of numerous targets in a single reaction.[13] This can translate to increased efficiency, yielding more data from each reaction and using fewer reagents. However, efficient multiplex reactions are difficult to design as assay conditions must be optimised to detect all targets equally.[13] A number of multiplex RT-PCR tests have been CE-marked for use in the EU.

Newer, real-time RT-PCR-based near-patient IVD tests that incorporate nucleic acid extraction, amplification and detection together into an integrated and sealed cartridge processing have been developed (Figure 1, C and D).[10] These rapid PCR devices increase the speed and convenience of PCR to support timely and accurate diagnosis. However, these near-patient tests are not currently available in Ireland, nor are they suitable for high-throughput testing.

Other molecular methods – isothermal amplification

By obviating the need for thermal cycling, isothermal amplification methods are simpler and faster to perform than RT-PCR, making them more suitable for resource-limited or near-patient testing applications. The RNA-targeting clustered regularly interspaced short palindromic repeats (CRISPR) associated enzyme Cas13 has recently been adapted for the isolation of gene segments for diagnostics using gene editing techniques.[7, 14, 15] Zhang et al. first reported a CRISPR-based nucleic acid detection technique called SHERLOCK (Specific High Sensitivity Enzymatic Reporter UnLOCKing) for the detection of SARS-Cov-2 nucleic acids.[7] A recently developed assay, SARS-CoV-2 DETECTR, is reported to have comparable accuracy to real-time RT-PCR. Methods using CRISPR Cas12 systems are in development, but are not currently used in a clinical setting.[14, 16]

Loop-mediated isothermal amplification (LAMP) detects viral nucleic acid through RNA amplification using four-to-six specially designed primers and a DNA polymerase

with chain displacement activity under a constant temperature (60-65°C).[17] LAMP can be combined with reverse transcription (i.e., RT-LAMP), where both reverse transcription and amplification occur simultaneously allowing the direct detection of RNA.[17] This system, can be coupled with a colorimetric indicator present in the reaction mix allowing readout of the amplification reaction and diagnosis based on an observed colour change. The diagnostic test accuracy of RT-LAMP based methods are reported to be similar to RT-PCR.[18] The technique is said to be highly specific as recognition of multiple conserved regions is required. RT-LAMP is a faster and more convenient method for SARS-CoV-2 RNA detection requiring fewer laboratory resources and has the potential to extend the capacity of laboratories to process 2.5 more clinical samples relative to qRT-PCR.[19] No CE-marked RT-LAMP technologies have been identified, although a number are reported to be in development.

Genetic sequencing

Genome sequencing was used primarily in the early days of the outbreak for initial identification of the novel virus and is largely a tool of viral discovery.[6] Now that the complete genome sequence of SARS-CoV-2 has been obtained, most sequencing is being undertaken to characterise the virus and monitor for viral mutation, not for clinical diagnosis.[6] Characterising the virus and genomic surveillance can be used by public health authorities to understand the genetic determinants of viral transmission, infectivity and virulence.

As SARS-CoV-2 has not previously been identified in humans, there is no acquired immunity to the virus within the population. Genomic surveillance will be useful in determining the genomic stability of SARS-CoV-2 and the likelihood that antibodies generated against the virus through exposure will provide protection against re-infection in the future. In response to the host immune response, selective pressure on the virus may result in antigenic drift over extended periods of time. Ongoing genomic surveillance will be important in monitoring for the appearance of selectively advantageous mutations. Viral genome sequences could also inform the development of treatments and vaccines.

2.3.2. Antigen detection tests

Immunoassays can be used to detect the presence of proteins in clinical samples. Detection of viral protein (termed antigen assays) indicates the presence of viral infections.[20] Immunoassays are available in a wide range of different formats, but essentially consist of an antigen or antibody, immobilised on a surface, which binds virus-specific antigens or antibodies from a patient sample (for example, sputum or blood sera). By adding a further reporter protein, it is then possible to detect a virus-specific immune signal to confirm the presence of the antigen or antibody.[20, 21] Binding assays such as immunofluorescence assays (IFAs) and enzyme-linked

immunosorbent assays (ELISAs) could be used for the diagnosis of SARS-CoV-2.[22, 23]

Antigen detection is well established in the investigation of some infections where diagnostic methods have evolved over decades (for example, hepatitis B virus), notably where it allows active infection to be differentiated from a vaccine-induced antibody response.[24] Assays which combine detection of antigen and or antibody allow earlier diagnosis of infection than assays detecting antibody alone, reducing the diagnostic window. This approach is in routine use for the diagnosis of viral infections such as HIV, where diagnostic approaches have evolved over decades.[25]

Antigen detection tests detect virus-specific antigens by using antibodies developed in the laboratory (the antibody does not come from the patient). The tests can detect the presence of infection during the acute stage of infection and could potentially be used in addition to current RT-PCR-based testing. They have a faster turnaround time, and are easier to operate relative to RT-PCR; however, they generally are less accurate.[26]

Antigen detection assays, if proven to have high sensitivity and specificity may be of value in the diagnosis of COVID-19 infection.

2.3.3. Viral culture

SARS-CoV-2 can be isolated from clinical samples through viral culture, but is not recommended as a routine diagnostic procedure.[4]

2.3.4. Microarray or microfluidic lab-on-chip technologies for the detection of viral RNA or antigens

New techniques such as high-density nucleic acid arrays, also known as microarrays or chips, are miniaturised devices, which comprise small flat surfaces, onto which ordered arrangements of individual samples are positioned, allowing simultaneous detection and identification of multiple viruses in a single clinical sample.[27, 28] Microarray-based methods allow the use of smaller sample volumes, more efficient analyses and higher throughput.[7] In clinical diagnostics, microarray technology can be used to differentiate between COVID-19 and other respiratory infections that have similar symptoms. Microarray technology for the detection of SARS-CoV-2 in addition to other common human respiratory pathogens are in development.

Microfluidics devices perform chemical analyses of extremely small volumes of fluids such as blood. The main advantage of microfluidic technologies is less sample and reagent consumption, in addition to their potential use as near-patient devices. Microfluidic systems have been used for the detection of other coronaviruses and are currently in development for the detection of SARS-CoV-2.[29]

2.4. Detection of immune response

2.4.1. Antibody tests

Humoral immunity refers to the production of antibodies in response to the presence of antigens in the blood or extracellular fluid. Antibody tests can therefore be used to detect past exposure to SARS-CoV-2. However, it typically takes the body a number of days to mount a response to the infection, so the utility of antibody tests for diagnosing acute infections in the early stages of the disease is limited. A positive test can indicate current or resolved infection; however, as noted, negative results do not exclude SARS-CoV-2 infection, particularly among those with recent exposure to the virus.

Antibodies against common human coronaviruses are prevalent in the population. Whole genome sequencing has shown that SARS-CoV-2 shares a high degree of nucleotide identity with SARS-CoV–2.[9] Thus, any antibody tests to detect SARS-CoV-2 needs to identify and rule out cross-reactivity with these common human coronavirus strains.[22]

Antibody-based methods detect the presence of IgG and IgM antibodies specific to SARS-CoV-2 in clinical samples. During the primary response to a virus, IgM antibodies are the first to appear, but are relatively short-lived and disappear after a number of weeks. The detection of IgM antibodies might imply recent or potentially active infection. IgG is the major antibody of the immune response and may provide long-lasting immunity against re-infection with the same virus.[30] While some studies have reported detection of antibodies three days after the onset of symptoms using antibody assays,[31] such tests may not be reliable in the early phase of infection and should not be used for case detection in patients with clinically suspected COVID-19 according to WHO guidance.[4] For the diagnosis of acute infections, there is considerable lag period as antibodies specifically targeting the virus typically appear seven to 14 days after illness onset.[32] Antibody production may be delayed, weak or ineffective in the elderly and in those who are immunocompromised as a result of disease, immunosuppression or other treatments which weaken the immune response, such as chemotherapy.

Immunoassays are typically easier to operate and have faster turnaround times compared with RT-PCR; however, in general, this is at the expense of diagnostic test accuracy.

2.4.2. Microarray or microfluidic technology for the detection of antibodies

The development of protein chip or microarray technology could provide a sensitive, high-throughput method for diagnosis of COVID-19 by facilitating detection of SARS-

CoV-2 antibodies in patient samples. The patient sample (for example, serum) is incubated on the chip. If SARS-CoV-2 antibodies are present in the sample, the interaction between the antibody and its target antigen is detected.[33]

Proteome microarrays for the detection of SARS-CoV-2 are currently in development and could be used to identify, profile, and compare specific antibody responses in patient sera to inform vaccine development, or screen viral antigens to find and characterise immunodominant epitopes for in-vitro diagnostics research.[34, 35]

2.5. Rapid tests

Rapid tests are defined under the common technical specifications for IVDs as qualitative or semi-quantitative in vitro diagnostic medical devices, used singly or in a small series, which involve non-automated procedures and have been designed to give a fast result.[36] Rapid tests are intended for use in resource-constrained or near-patient settings, with their use restricted to the setting for which CE marking was received. While other commercial CE-marked tests automated for use on analyser machines are available in portable equipment form and provide fast results, they do not fall under the above definition of rapid tests.

In February 2020, a WHO expert group identified accelerated research into rapid tests as one of eight key actions necessary to the control the COVID-19 emergency.[37] Many of the rapid tests available and in development for the detection of SARS-CoV-2 are based on antigen and antibody immunoassays. The majority of rapid tests are based on lateral flow assays, cellulose-based devices intended to detect the presence of a target analyte in a liquid sample.[38] As highlighted previously, with antibody and antigen-based tests there is a potential for cross-reactivity to proteins common to other types of coronavirus. Reliable measures of the diagnostic test accuracy of newly developed tests will require independent validation studies.[22]

Rapid tests based on isothermal nucleic acid amplification that can provide timely results to clinicians have also been developed. At least one test has been approved under an emergency use authorization (EUA) in the US and commercialised. While not yet CE-marked, this test is undergoing independent validation testing in Ireland. The test, which can provide results within 45 minutes, leverages off an existing cartridge technology in which multiple regions of the viral genome are targeted. It is designed for use on a platform that has already been deployed in a number of hospitals.[39]

Technological advancements in immunoassays are not necessarily in the methodology of the assay, but rather the instrumentation used to interpret the results. Results obtained through visual inspection are less sensitive and subject to

inter-operator variability. The use of digital readers allows a lower limit of detection than can be achieved with manual interpretation of the assay and increases the reproducibility of results. However, digital immunoassays require increased operator handling, and the availability of the assay reader wherever the test is carried out.[40]

2.6. Selection and interpretation of tests

Selection of the most appropriate testing strategy will depend on the local epidemiological situation and the availability of resources. The ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) criteria proposed by the WHO can be used as an indicator of the most appropriate diagnostic test(s) among available testing alternatives in resource-constrained settings.[41] While efforts are underway increase diagnostic testing capacity for SARS-CoV-2, selection of the most appropriate test is challenging for policy-makers, laboratories and other end users given the current global shortage of laboratory consumables and reagents, and limited independent test validation data for. The selection and interpretation of tests is discussed further in Section 3 (international approaches) and Section 4 (operational utility) of this assessment.

Real-time RT-PCR is the gold standard for diagnosing suspected cases of COVID-19. Notwithstanding this, it is noted that negative test results do not preclude SARS-CoV-2 infection and cannot be used as the sole basis for patient management decisions. There may be a number of explanations for apparent discordance between test results and clinical findings, some of which are unrelated to the test itself. Firstly, there is a potential for pre-analytical errors including issues such as insufficient sampling, contamination of specimens, and inappropriate storage and transport conditions. Secondly, the analytical process can effect results due to operator error or the use of different sample preparations. Thirdly, the viral dynamics of SARS-CoV-2 across the time course of the infection are still not fully understood. Hence, false negative test results may occur if samples are tested during the early incubation period or else during the late convalescent phase, when virus levels may be undetectable. Differences in viral dynamics over the course of an infection may also contribute to discordance between test results based on different specimens (upper versus lower respiratory tract).

Testing in accordance with the principles of good laboratory practices and quality assurance programmes for clinical laboratory testing will minimise the risk of false negative or false positive results. This includes application of appropriate assay controls that identify poor-quality samples can help to avoid many false-negative results as a result of improper collection, storage and handling procedures.

In relation to the RT-PCR test, there may be differences in primers and probes used in the protocols underpinning the RT-PCR methods that impact analytical sensitivity

and specificity, while different laboratories and devices may use different threshold values to determine positive, negative and indeterminate test results, which may lead to false-negative results as samples may be interpreted slightly differently.[42, 43] Improvements in RT-PCR tests are ongoing to enable better detection at lower levels of RNA.

Table 2.1 Characteristics of alternative diagnostic tests for SARS-CoV-2

Method	Use	Suggested advantages	Suggested limitations/challenges	Estimated time*	Potential use(s)
CE-marked and commercially available					
RT-PCR	Detection of viral RNA	• Accurate • Widely available • Gold standard technique • Well established technology • Multiple clinical applications (e.g. diagnostics, screening, treatment decisions, monitoring of response to treatment). • Validated protocols available	• Requires specialised laboratory equipment and facilities • Requires skilled analysts • Cannot identify those who have cleared the infection • May not recognise viral mutations • Requires high purity samples • Misclassification errors can occur due to the timing or site of sampling	Reaction time: 4-6 hours minimum Turnaround time: 24 hours[44]	• Detection of active infection • Multiplex RT-PCR can be used for differential diagnosis
Microfluidic assays	Perform chemical analyses on small volumes of fluids e.g. blood	• Less sample and reagents consumption than RT-PCR • Potential to analyse more pathogens within a single test (e.g., respiratory panels)	• Newer technology • Not independently validated	Reaction time: 40 minutes	• May be suitable for near-patient testing or resource-constrained settings
Antibody tests	Detection of IgG or IgM antibodies.	• Identify those who have previously been infected • Rapid tests (turnaround < 30 minutes) available	• Antibody response may not be seen for 8-10 days, so not suitable for identifying active infection • Potential for cross reactivity with other viruses	Reaction time: 2-30 minutes	• Seroepidemiological studies • Inform public health measures to limit virus spread • De-escalation of care for hospitalised patients • Redeployment of healthcare or other essential workers • Can be used for near-patient testing
Antigen detection tests	Identification of viral proteins	• Faster turnaround time compared with RT-PCR • Relieve pressure on laboratories • Antigens are more stable than RNA	• Less accurate and reliable compared with RT-PCR • Variation in performance between devices	Reaction time: 10 minutes.	• Identification of active infection • Triaging of patients • Can be used for near-patient testing

Method	Use	Suggested advantages	Suggested limitations/challenges	Estimated time*	Potential use(s)
Available for research use only					
Whole genome sequencing	Characterisation of the viral genome	• Understand the spread of the virus	• Costly • Time-consuming	Turnaround time: 7 hours[45]	• Virus characterisation • Research and genomic surveillance • Understanding viral transmission and pathogenicity • Identification of viral mutations • Inform treatment development
In development					
CRISPR	Gene editing technology	• Accurate • Fast	• Newer technology - not yet independently validated.	Reaction time: 30 - 60 minutes[14-16]	• Detection of active infection • Near-patient and lab-based applications
Isothermal nucleic acid amplification technologies e.g. RT-LAMP	Detection of viral RNA	• Faster than RT-PCR • Accurate • Simpler and cheaper instrumentation • More robust to inhibitors present in some sample preparations than RT-PCR (i.e. less stringent sample processing is necessary)	• Requires heat block/water bath/incubator for isothermal amplification of RNA. • Newer method - not yet independently validated.	Reaction time: 40 minutes[17-19, 46-49]	• Detection of active infection • Suitable for resource-constrained settings
Microarray assays	Detection of multiple viral components (e.g. RNA or protein) simultaneously	• Test for the presence of multiple common human respiratory viruses and bacteria simultaneously • Medium to high throughput • Less sample and reagent consumption than RT-PCR • Fewer operational requirements than RT-PCR • Reduced cost per reaction	• Reaction time means it cannot be used to inform rapid clinical decision-making • Target viral sequences must be specific to each viral strain to prevent cross-hybridization to multiple related genome sequences	Turnaround time: 2-5 hours[50, 51]	• National centres for infectious disease control • Differential diagnosis • Rule-out bacterial infection or co-infection with other viruses • Confirmation of results from rapid tests

Key: CRISPR - targeting clustered regularly interspaced short palindromic repeats; IgG – immunoglobulin G; IgM - immunoglobulin M; RNA - ribonucleic acid; RT-LAMP – reverse transcription loop-mediated isothermal amplification; RT-PCR - reverse transcription polymerase chain reaction.

**Notes: ***Estimated reaction times (i.e. the length of time required to carry out a test excluding sample preparation) and turnaround times (i.e. the length of time between receipt of the sample in the laboratory to reporting of the result) are based on manufacturer data from CE-marked tests, where available. For newer technologies, estimates are based on tests in development or results from pre-print studies.

3. International approaches to diagnostic testing

Key points

- The WHO, ECDC, and the CDC in the US recommend using laboratory-based nucleic acid amplification (molecular) tests (manual or automated) to detect SARS-CoV-2 RNA in clinical specimens (as of 14 April 2020). The same molecular approach has been recommended for use to detect acute infection with SARS-CoV-2 in Ireland and the UK, among other countries.

- The ECDC recommends that a serum sample should be collected and stored during the acute phase of illness (that is, after symptom onset), and again two to four weeks later, during the convalescent phase, to gain a better understanding of disease course; for example, time to seroconversion and subsequent viral clearance.

- The WHO has advised against the use of rapid diagnostic tests based on antigen detection and host antibody detection in any setting (except research settings), including for decision-making, until evidence supporting their use for specific indications is available.

- Microfluidic lab-on-chip technologies and full genetic sequencing do not appear to be used in any country for the detection of COVID-19. Although not yet CE-marked, a microarray respiratory panel incorporating SARS-CoV-2 is reported to be in use in the UK. While CRISPR is a gene-editing technology, because of technical similarities in the process, a number of CRISPR laboratories are reported to have repurposed their resources to provide additional COVID-19 testing capacity during this pandemic.

A brief scoping review was undertaken to identify the diagnostic approaches being recommended internationally. Included in the review were international agencies and a limited number of European and non-European countries. This section presents the findings from the review.

3.1 International guidance

A summary of the international guidance on testing is provided in Table 3.1. As of April 1 2020, the WHO,[52] ECDC,[53] and the CDC in the US[54] recommend using laboratory-based nucleic acid amplification (molecular) tests (manual or automated) to detect SARS-CoV-2 RNA in clinical specimens. In each case, the recommended approach to testing is broadly consistent. A sample from the upper and or lower

respiratory tract is taken using a nasopharyngeal or oropharyngeal specimen (upper respiratory tract), often using the same swab, and or endotracheal, bronchoalveolar or sputum specimen (lower respiratory tract). A nucleic acid amplification test, or RT-PCR, is then used to identify the RNA specific to SARS-CoV-2 that cause COVID-19. In Ireland[55] and the UK,[56] among other countries,[57-59] the same molecular approach has been recommended for use to detect COVID-19. As of 11 April 2020, Spain has also issued guidance on which samples (that is, upper or lower respiratory tract) should be used for the diagnosis of COVID-19 by rapid antigen testing, although it is unclear whether the test is routinely used in practice.

Although an increasing number of alternative diagnostic tests are being developed and commercialised, there remains considerable uncertainty regarding the clinical performance of these tests, in particular rapid tests such as direct SARS-CoV-2 antigen detection and indirect antibody detection tests. The limitations of rapid diagnostic tests are being assessed by WHO referral laboratories and in clinical studies funded by the European Commission and EU member states.[36] The WHO has advised against the use of rapid diagnostic tests based on antigen detection and host antibody detection in any setting (except research settings), including for decision-making, until evidence supporting their use for specific indications is available.[60] The WHO and ECDC have noted that they will update their guidance on testing once there are sufficient data to validate the accuracy of the tests, including guidance on when they should be deployed in the clinical pathway.[36]

While the use of alternative diagnostic testing to RT-PCR approaches remains to be endorsed by the WHO and ECDC, or to the best of our knowledge at a national level by any country, there has been a shift in guidance towards additional testing pending the availability of validated tests. The ECDC,[53] along with many countries, including Australia,[58] Germany,[59] Spain,[57] and the UK,[56] recommend collecting serum samples for later detection of antibodies to SARS-CoV-2, once validated serological assays are available (Table 3.1). The ECDC recommends that a serum sample should be collected and stored during the acute phase of illness (that is, after symptom onset), and again two to four weeks later, during the convalescent phase. In order to gain a better understanding of the disease course, these data will be particularly helpful in determining the time to seroconversion.[61]

Seroprevalence data could help to identify the level of population immunity, and inform the allocation of scarce resources to prevent or manage transmission. On a larger scale, serological testing plays an important role in determining the extent of viral spread in the community. A proportion of the population may already be immune due to mild or asymptomatic infections. In this way, serological testing could inform practical issues, such as whether it is appropriate to re-open schools and non-essential services closed to limit community transmission of the virus, or

allow healthcare workers, along with non-healthcare workers, to return to work. However, such an approach would be resource-intensive. Section 4 elaborates on the issues associated with serological testing in practice.

Microfluidic lab-on-chip technologies and genetic sequencing do not appear to be used at a national level in any country for the detection of COVID-19. Although not yet CE-marked, a microarray respiratory panel incorporating SARS-CoV-2 is reported to be in use in the UK. CRISPR is a gene-editing technology, which in recent years has also been used for the in vitro detection of nucleic acids. However, diagnostic tests employing CRISPR are as yet still only in the development phase. Because of technical similarities in the process, a number of CRISPR laboratories are reported to have repurposed their resources to provide additional COVID-19 testing capacity during this pandemic. However, as indicated in Section 2.4.1, genome sequencing is only useful during the early days of an outbreak. In the UK, the COVID-19 Genomics UK Consortium, comprising the NHS, Public Health England, UKRI, and Wellcome has been launched to track viral spread and evolution via genome sequencing of SARS-CoV-2 samples.[62] Samples from patients with confirmed cases of COVID-19 will be sent to a network of sequencing centres in order to monitor changes in the virus at a national scale to understand how the virus is spreading and whether different strains are emerging.[17]

While RT-PCR remains the primary test for the detection of SARS-CoV-2 internationally, there has been a number of recent developments in relation to the development and use of alternative diagnostic testing approaches to detect the virus, as discussed below.

3.2 Recent international developments in diagnostic testing

A substantial number of RT-PCR detection kits have been authorised for use and commercialised internationally. An advantage of using these test kits, in particular rapid PCR detection kits, is that they can increase the speed and convenience of PCR to support timely and accurate diagnosis of COVID-19. Use of these tests also provides an opportunity to optimise and expand testing if deployed in laboratory settings where they can leverage off existing laboratory resources such as reagents, primer sequences, and automated systems. Some rapid PCR-based test kits have also been developed and can be deployed near the point-of care with minimal training required; however, these kits do not have the same capacity, or throughput, as laboratory-based test kits. They are also not yet currently available in Ireland, to the best of our knowledge.

Given the large number of rapid tests (and in particular rapid antibody tests) that have been commercialised for use, it is likely that there has been some uptake and use of these alternate tests. The settings and context in which they are being used

is, however, uncertain. In the UK, it has been reported that rapid antibody tests will be rolled out, alongside rapid antigen tests, to address the next phase of the COVID-19 pandemic.(63) On April 9 2020, the Medicines and Healthcare products Regulatory Authority (MHRA) in the UK published specification criteria for serology near-patient tests and self-tests.(64) These criteria outline the minimally (and sometimes preferred) clinically acceptable specifications for SARS-CoV-2 tests to be used in the UK during the COVID-19 pandemic, highlighting that use of lower specification test kits would likely provide no clinical benefit and could lead to increased harm. Public Health England currently advises against the use of these tests in community settings, such as pharmacies, or at home due to the lack of evidence on the suitability of the tests to detect COVID-19 in these settings.(65) The Health Products Regulatory Authority (HPRA) in Ireland has also advised the public against the purchase of diagnostic test kits online or from any retailer after it became aware of falsified test kits being sold in Europe.(66)

On 15 April 2020, the European Commission issued guidelines on COVID-19 IVD tests and their performance.(67) The Commission subsequently published a working document that provides additional guidance to the legally obligatory requirements defined in the IVDR.(68) Based on the principles of good analytical (testing) practice, and making the distinction between a tests analytical performance (that is, the ability of the test to detect a marker of interest) and its clinical performance (that is, the ability of a test to determine a patient's clinical status), these guidelines include performance criteria for RT-PCR, antigen-based and antibody-based tests. The current absence of control samples and reference materials are noted as a particular challenge to establishing the diagnostic test accuracy of antigen and antibody tests.(68) The Commission has also established a European taskforce comprising representatives of the European Commission's Joint Research Centre (JRC), ECDC, HTA experts and IVD experts. This taskforce is aimed at supporting the JRC in completing a rapid review of the performance of IVD test methods and devices for the assessment of COVID-19 and to make recommendations regarding same.(67) While common technical specifications (CTS) exist for a number of blood tests (blood grouping tests, HIV tests), as yet no such CTS exist for COVID-19.(69)

While antibody testing is unsuited to the detection of acute infection, it has been suggested that targeted antibody testing could provide key data for efforts to model the course of the pandemic and the necessary public health response. If validated antibody tests were available, there is speculation that they could be used to enable rollout of so-called immunity passports that would enable social restrictions to be lifted and inform staff redeployment. There are anecdotal reports that a number of healthcare organisations in the US have commenced, or plan to roll out, antibody testing to inform deployment of healthcare staff. A number of these institutions have internally developed tests that have undergone rigorous internal verification to

ensure their accuracy.[70] There are also anecdotal reports that antibody testing to inform deployment of healthcare staff has commenced in two regions in Italy. In Germany, the Helmholtz Centre for Infection Research (HZI) is coordinating a study to determine if there is unidentified COVID-19 immunity in the population using antibody tests. Over 100,000 subjects are to participate in the population study which will provide greater insights into the extent of viral spread and potential immunity in the population.[71] Of note, immunity passports are not used for any other respiratory virus, so their role in SARS-CoV-2 remains theoretical for now.

A number of clinical trials are underway internationally to address potential immunity in the population,[72] along with time to seroconversion,[73] which could also provide key data for efforts to model the course of the pandemic in the future. However, the majority of these trials are collecting serum samples for the later detection of COVID-19, once serological testing has been validated.

3.3 Discussion

Internationally, real-time RT-PCR remains the primary recommended test for the detection of the SARS-CoV-2 virus. A range of alternative diagnostic testing approaches have been developed to detect either the virus or the body's immune response to the virus. These include a range of laboratory-based and rapid tests designed for near-patient testing; however, the majority of these are yet to be validated for use in clinical settings. As of 8 April 2020, the WHO has strongly advised against the use of rapid diagnostic tests based on antigen detection and host antibody detection in any setting, except research settings, until the evidence base is sufficient to justify their use.

Table 3.1 Testing approaches for SARS-CoV-2 by organisation and country

Organisation / country	Primary SARS-CoV-2 test	Sample(s)	Specimen(s)	Additional tests for SARS-CoV-2
WHO[52] 19/03/2020	Nucleic acid amplification test	• Upper respiratory tract sample and/or lower respiratory tract sample	• Upper (ambulatory patients): - nasopharyngeal and oropharyngeal swabs - nasopharyngeal wash/aspirate • Lower (patients with more severe respiratory disease): - sputum - aspirate - lavage	Suggests the use of nucleic acid sequencing for confirmation of cases of COVID-19 when necessary
CDC[54] 14/04/2020	Nucleic acid amplification test	• Upper respiratory tract sample	Nasopharyngeal swab (recommended) If this is not possible: • Nasal mid-turbinate (NMT) swab (using a flocked tapered swab); • Anterior nares specimen (using a flocked or spun polyester swab)	Also recommends using lower respiratory tract specimens, if available, including sputum. When it is clinically indicated (e.g., those receiving invasive mechanical ventilation) a lower respiratory tract using aspirate or bronchoalveolar lavage sample is recommended
ECDC[53] 08/02/2020	Nucleic acid amplification test	• Upper respiratory tract sample; • Lower respiratory tract sample if the patient is hospitalised or in intensive care	• Upper: - Nasopharyngeal swab - Oropharyngeal swab - Nasopharyngeal wash/aspirate. • Lower (if patient is hospitalised or in intensive care): - Bronchoalveolar - Sputum - Aspirate	If resources allow, a single positive test should be confirmed by a second RT-PCR assay targeting a different SARS-CoV-2 gene. If the result of the first virus gene test is inconclusive or weakly positive and there is a strong suspicion for SARS-CoV-2 infection, another specimen should be tested with the primary and secondary RT-PCR assays. Serum (to be stored pending serology availability), acute and convalescent (possibly 2 to 4 weeks after acute phase), along with faeces

Table 3.1 Testing approaches for SARS-CoV-2 by organisation and country

Organisation / country	Primary SARS-CoV-2 test	Sample(s)	Specimen(s)	Additional tests for SARS-CoV-2
Ireland[55] 20/03/2020	Nucleic acid amplification test	• Upper respiratory tract sample; • Lower respiratory tract sample	• Upper: - Combined swab for oropharyngeal or nasopharyngeal samples (one swab to test both is sufficient) in ambulatory patients. • Lower: - Bronchoalveolar lavage OR Endotracheal aspirate OR Sputum (if produced) is preferred in cases of severe illness	None specified
UK[56] 06/04/2020	Nucleic acid amplification test	• Upper respiratory tract; • Lower respiratory tract	• Upper: - A viral nose swab AND a viral throat swab in one collection tube OR - single swab used for throat then nose in one collection tube OR - A nasopharyngeal aspirate in a universal transport pot. Bacterial or charcoal swabs are not suitable • Lower: - Sputum, if available	A serum test should be collected if a patient is admitted to hospital. The sample should be collected at the same time as other samples collected for primary diagnostic testing for COVID-19
Australia[58] 01/04/2020	Nucleic acid amplification test	• Upper respiratory tract sample; • Lower respiratory tract sample, where possible • Serum (to be stored pending serology availability)	• Upper: - Deep nasal and oropharyngeal combined swab - Nasal wash/aspirate • Lower (recommended where possible): - Bronchoalveolar lavage - Sputum	Serum should be collected during the acute phase of the illness (preferably within the first 7 days of symptom onset), stored, and when serology testing becomes available tested in parallel with convalescent sera collected 3 or more weeks after acute infection. If no acute sample was collected, sera collected 14 or more days after symptom onset may be tested
Germany[59] 30/03/2020	Nucleic acid amplification test	• Upper respiratory tract sample; • Lower respiratory tract sample, where possible	• Upper respiratory tract: - Nasopharynx smear or lavage - Oropharynx smear • Lower: - Bronchoalveolar lavage - Sputum (produced or induced according to instructions ; observe occupational safety) - Tracheal secretion	Serum samples should be collected and preserved as early as possible in the acute phase in order to check seroconversion for SARS-CoV-2 by pairing with convalescent serum

Table 3.1 Testing approaches for SARS-CoV-2 by organisation and country

Organisation / country	Primary SARS-CoV-2 test	Sample(s)	Specimen(s)	Additional tests for SARS-CoV-2
Spain[57] 11/04/2020	Nucleic acid amplification test or rapid antigen test	• Upper respiratory tract sample; • Lower respiratory tract sample, where possible	• Upper: - Nasopharyngeal swab (preferred) and/or oropharyngeal swab • Lower (if patient is hospitalised or in intensive care): - Bronchoalveolar (preferred) and/or - Aspirate	If possible, serum samples should be taken at least 14-30 days apart, with the first serum collected in the first week of illness(acute phase). If only a single serum sample is collected, it should be taken at least 14 days after the onset of symptoms in order to confirm the presence of specific antibodies

4. Operational utility

Key points

- Pathogen detection tests and tests aimed at detecting an immune response to the virus should not be considered competing alternatives. Both testing approaches are clinically relevant at different time points during the clinical course of infection.
- Nucleic acid amplification-based (molecular) approaches for the detection of the SARS-CoV-2 RNA are important for confirmation of acute viral infection early in the clinical course of infection.
- Once validated rapid antigen tests, with sufficient sensitivity and specificity, are available, they could be used alongside real-time RT-PCR in the acute phase of infection, in circumstances where access to or turnaround times for laboratory-based testing is inadequate and an early diagnosis if required to inform patient care.
- The use of antibody tests is limited to later in the clinical course of infection or following recovery to identify those who have been exposed to SARS-CoV-2. Their use is contingent on the availability of validated tests with sufficient sensitivity and specificity. As SARS-CoV-2 has not been previously identified in humans, little is known regarding the adequacy of the immune response or the duration of immunity following seroconversion, so it is not known if reinfection can occur. The role of antibody testing is therefore limited outside of well-constructed seroprevalence studies to model the course of the pandemic and inform the public health response.
- The level(s) at which rapid antigen or antibody tests might be deployed has important implications for both administration and reporting of tests as well as the overall governance of any testing strategy.
- The currently agreed national testing strategy is outlined in the HSE pathway of care for the assessment and management of COVID-19. This document is routinely updated as the strategy evolves based on emerging evidence.

4.1 Introduction

This section summarises where available tests, and particularly:

- pathogen detection tests (to detect active infection with the SARS-CoV-2 virus)

- tests to detect an immune response to the virus (that is, anti-SARS-CoV-2 IgG and IgM antibodies that indicate past exposure to the virus),

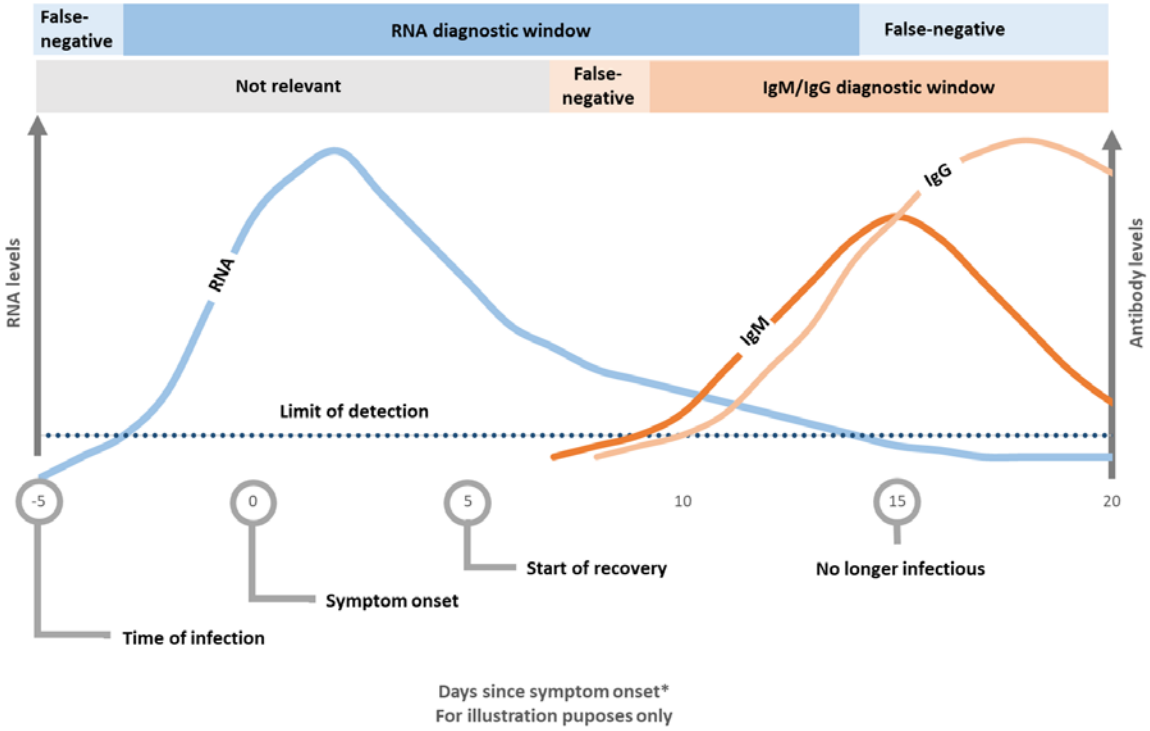
could be deployed in the clinical pathway in the management of COVID-19.

Viral antigens and antibodies become detectable at different times during the clinical course of infection (that is, from the presymptomatic/asymptomatic phase through to full resolution of symptoms or death). While the exact time at which SARS-CoV-2 RNA, specific antigens, and IgG and IgM antibodies can be detected depends on several factors, including the specific test used, individual patient variability and viral characteristics. In general, the stages at which these markers of infection become detectable can be estimated to inform the use of diagnostic tests. Information regarding the optimal timing of tests measuring viral antigens or components of the host immune response is vital to inform the optimal timing of requests for tests and interpretation of test results.

In general, methods detecting the presence of the virus, and methods based on the detection of the host immune response, are appropriate at different points in the clinical course of infection for different clinical and public health applications. For the purposes of this report, operational utility is used to describe the extent to which application of a diagnostic test can produce clinical benefit by preventing or improving adverse health outcomes through the detection of current or past SARS-CoV-2 infection.

The diagnostic windows for the detection of acute SARS-CoV-2 infection (viral RNA) and the immune response (anti-SARS-CoV-2 IgM and IgG) indicating past exposure to SARS-CoV-2 are summarised in Figure 4.1. Where appropriate, evidence generated as part of 'evidence summaries' compiled by HIQA to assist the Clinical Expert Advisory Group supporting the NPHET in their response to COVID-19 has been used to determine the operational utility of identified diagnostic testing methods during the clinical course of disease (that is, from the pre-symptomatic phase or early infection through to full resolution of symptoms).[74]

Figure 4.1 Diagnostic windows for the detection of acute SARS-C0V-2 infection (viral RNA) and the immune response (anti-SARS-CoV-2 IgM and IgG) indicating past exposure to SARS-CoV-2



Note: ***While the sequence of events is well understood, the exact timeline is based on early evidence summaries and is subject to considerable uncertainty.

4.1. Methods of viral detection for acute infection

Early detection of cases is a priority to minimise COVID-19-associated morbidity and mortality, initiate rapid and effective contact tracing and prevent further transmission of the virus.

Using RT-PCR, SARS-CoV-2 viral RNA can be detected one-to-two days prior to symptom onset in upper respiratory tract samples.[75] The evidence to date appears to suggest that viral load throughout the duration of COVID-19 peaks around symptom onset and decreases within one-to-three weeks.[74] Although the duration of detection and the magnitude of the viral load, appears to vary from patient to patient, there is evidence to suggest that the viral RNA becomes undetectable (from upper respiratory tract specimens) approximately two weeks following symptom onset.[76-90] Therefore, based on current data it is estimated that the infectious period lasts for seven-12 days in moderate cases and up to two weeks on average in severe cases.[91]

Other nucleic acid based approaches for the detection of SARS-CoV-2 nucleic acids such as CRISPR/Cas12 and RT-LAMP-based methods have been reported to demonstrate

comparable sensitivity and specificity in proof-of-principle studies to RT-PCR suggesting that these assays may be most appropriately used early after symptom onset when viral load is highest. However, further independent validation studies using clinical samples are needed. (Figure 4.1). Antigen detection tests are also suitable for use at an earlier stage in the clinical course of infection.[26]

Early case detection

Molecular methods (for example RT-PCR, isothermal amplification-based methods) should be used for early detection of SARS-CoV-2 cases, where possible. In circumstances where molecular-based testing methods are not immediately available, validated antigen detection tests, if available, could be used in particular to facilitate early diagnosis in patients at the highest risk of adverse clinical outcomes, such as patients in intensive care units. However, negative results from antigen detection tests should be followed up with RT-PCR testing to confirm the absence of infection.

Patient discharge

There is some evidence to suggest that high serum viral loads may be associated with more severe disease.[92, 93] In the early days of infection, serial monitoring of the plasma viral load in COVID-19 patients with highly sensitive tests could be considered to provide prognostic insights and facilitate treatment decisions, although it is recognised that there are currently no specific medications to treat COVID-19. In the context of limited reagents and personal protective equipment needed for sample collection, in addition to an unmet demand for initial diagnostic tests, clinical monitoring of patients based on viral RNA or antigen levels may not be feasible. Where testing capacity permits, patients may be discharged based on clinical resolution of symptoms, and evidence for viral RNA clearance from the upper respiratory tract. However, the frequency of specimen collection may depend on local epidemic characteristics and resources. Current guidance from the WHO recommends that two consecutive negative results collected more than 24 hours apart from a clinically recovered patient are needed prior to hospital discharge.[94]

Differential diagnosis

Multiplex PCR testing is of particular importance in immunocompromised patients in whom co-infections are common and are associated with greater morbidity and mortality compared with immunocompetent individuals.[95] The use of multiplex PCR that test for the presence of multiple common human respiratory pathogens in parallel can facilitate differential diagnosis and enable timely, appropriate treatments to be initiated in selected patients.[96] While the current national emergency relates to the COVID-19 pandemic, and early evidence indicates that CT findings in COVID-

19 lung disease are highly suggestive of infection with SARS-CoV-2, it must be noted that acute respiratory signs and symptoms are seldom specific for a single pathogen. Ultimately, detection strategies that allow for multiple respiratory pathogens to be simultaneously detected, may have a significant impact on infectious disease management both from a patient and a public health perspective. The ability to accurately rule in or out a respiratory pathogen particularly in cases of severe infection leading to patient hospitalisation in the ICU supports optimised care and therapy selection for the individual patient.

Syndromic respiratory infection testing is used for seasonal and sporadic outbreak surveillance and preparedness and is routinely deployed as part of epidemiological surveillance by national centres for infectious diseases control. While still in development, multiplex PCR testing kits and microarray technology that also incorporate SARS-CoV-2 in the test panel of common respiratory pathogens will be required for the next influenza season to replace existing multiplex kits deployed in the healthcare system.

Patient triage

In the context of reagent shortages and inadequate access to laboratory testing, consideration could be given to the use of rapid antigen tests or rapid molecular tests to accelerate clinical decision-making and to reduce the workload of centralised testing laboratories. If accurate and validated tests become available, rapid tests, in particular antigen detection tests, could be used to triage or screen patients in healthcare settings.[97]

Prioritisation of case detection to reduce transmission

The agreed national testing strategy is outlined in the HSE pathway of care for the assessment and management of COVID-19.[98] This document is routinely updated as the strategy evolves based on emerging evidence. During the scaling-up of the testing capacity, a gradual approach based on clearly established priorities is necessary. Testing is prioritised for those most in need in order to minimise COVID-19-associated morbidity and mortality. High priorities for testing include healthcare workers, people with comorbidities, people in long-term care facilities and elderly individuals. If there is sufficient capacity within the healthcare system, prioritisation of testing may be expanded to holders of 'essential jobs' (such as social workers, public transport, transportation and distribution of essential goods, first responders etc), and those for whom working-from-home is not an option.

Decentralised rapid antigen or rapid molecular testing could be performed in near-patient or community settings without the need for specialised equipment. However, the impact of near-patient testing on workflow processes in a particular setting

requires careful consideration. Given the lower sensitivity of rapid antigen tests relative to RT-PCR (that is higher risk of false negatives), it is assumed that such tests should only be used to rule-in cases. That is, follow-up testing with RT-PCR or comparable molecular methods would be required to confirm a negative test result as it does not preclude SARS-CoV-2 infection and could not be used as the sole basis for patient management decisions. The availability and diagnostic test accuracy of CE-marked rapid antigen tests is discussed further in Sections 5 and 6. However, it is of note that although a number of rapid antigen tests have been reported as CE-marked, no data to support their independent validation has been identified.

Surveillance

Strategies for the surveillance of viral transmission are important to inform safe and effective infection control measures. An Irish Epidemiological Modelling Advisory Group has been established to inform public health measures in relation to COVID-19. National level surveillance data could be used to support the group in modelling the course of the pandemic. National level surveillance efforts are important for ongoing monitoring of:

- the number of new cases, geographic spread, and severity of COVID-19 in the population in order to estimate the burden of disease and assess the direction of recent time trends
- the risk groups that are most affected
- the impact of the pandemic the healthcare system to predict the trajectory of the pandemic curve and inform resource allocation
- the impact of any mitigation measures (for example, contact tracing, social distancing) to inform adjustments to the timing and intensity of infection control measures
- outbreaks in hospitals or long-term care facilities to protect healthcare workers and patients.

Data on those diagnosed with SARS-CoV-2 infection in Ireland is captured by current surveillance systems in Ireland. As testing capacity expands, more comprehensive estimates of viral transmission will become available.

Sentinel syndromic surveillance refers to monitoring of rate of occurrence of specific conditions in selected, targeted groups or networks (that is, sentinels) to estimate population-level incidence rates and trends. The ECDC has recommended that COVID-19 surveillance should be integrated with existing sentinel surveillance of influenza-like illness (ILI) or acute respiratory infection (ARI).[99] Where feasible, it has been suggested that these sentinel surveillance systems should be expanded to

include more physicians and thus improve population coverage to obtain more comprehensive estimates.[99] It is not yet known if SARS-CoV-2 will follow the traditional respiratory season with a decrease in the late spring and summer. Therefore it has been suggested that sentinel surveillance should be extended beyond the end of the influenza season in order to generate data in relation to COVID-19.[99]

Virological sentinel surveillance of COVID-19 should be based on the clinical specimens obtained through national sentinel surveillance of influenza-like illness / severe acute respiratory infections (ILI /SARI). Representative stains with associated geographic, demographic (for example, age, sex, comorbidities), clinical (such as disease severity) and temporal data should be selected for sequencing in order to monitor genetic changes in the virus that could alter the virulence of the virus or sensitivity to diagnostic tests.[99]

4.2. Methods detecting the host immune response

Antibody testing is dependent on the host's immune response to infection. The length of time this takes will depend on factors such as the severity of infection and the ability of the host's immune system to respond to infection. Therefore, antibody tests cannot be used to identify cases during the acute phase of infection. The timing of seroconversion for SARS-CoV-2 is said to be similar to or slightly earlier than in SARS-CoV infection.[80, 100] SARS-COV-2 IgG or IgM antibodies have been reported to become detectable at approximately 10 days after the onset of illness.[86, 101] However, seroconversion has been reported to occur at day six or seven after symptom onset in some cases.[85, 87] Larger studies have also indicated that for the majority of patients, seroconversion more typically occurs after day 10 (Figure 4.1).[102, 103]

As noted in Section 3, following rigorous internal verification to ensure their accuracy, a number of countries and providers are using laboratory-based antibody tests to inform decision-making. In the context of inadequate access to laboratory testing, rapid antibody tests may be used to reduce workload on centralised testing laboratories. In contrast to rapid antigen tests to detect active infection where the risk of a false negative test is of greater importance, the specificity of rapid antibody tests is critical, as a false-positive result could provide incorrect assurance that an individual is immune to SARS-CoV-2. The availability and diagnostic test accuracy of rapid antibody tests is discussed further in Sections 5 and 6. However, it is noted here that, while a large number of rapid antibody tests have been reported as CE-marked, no data to support their independent validation has been identified. None of the available CE-marked antibody tests are approved for self-testing.

Targeted antibody testing could provide key data for efforts to model the course of the pandemic and the necessary public health response. The operational utility of antibody testing can be considered in the context of three potential scenarios:

- Patient level testing to inform clinical management
- Cohort studies to inform staff deployment
- Population level seroepidemiological studies to inform public health strategies.

The level(s) at which such testing might be deployed has important implications for both administration and reporting of tests as well as well as the overall governance of any testing strategy.

Patient-level testing

It has been suggested that antibody testing could be used to inform the management of patients diagnosed with COVID-19. Current guidelines from the WHO recommend collection of both acute and convalescent serum samples from patients for serological testing, which can support the identification of the immune response to a specific viral antigen.[4] Decisions to de-escalate care for patients hospitalised with COVID-19 patients could be informed by antibody testing to document IgG antibody specific to SARS-CoV-2 in addition to evidence of viral clearance and clinical improvement.

The use of testing to inform the care and management of an individual patient, should be conducted in accordance with routine administration and governance arrangements. That is, the testing, reporting and follow up remain the responsibility of the patient's healthcare provider.

Cohort studies to inform staff deployment

Given the current international emergency in terms of the COIVD-19 pandemic, it has been suggested that testing of individuals with suspected past exposure to SARS-CoV-2 could be used to inform staff redeployment and or allocation of staff resources.[61] As noted in Section 3, it has been suggested that immunity passports could be issued to those with evidence of a sufficient acquired immune response to inform the eligibility of staff to return to work. It has also been suggested that, in the context of healthcare workers, these staff could be preferentially employed in high-risk areas as they would not be considered at risk of contracting or spreading the disease.[61] While neither of these approaches have previously been adopted, the approach is in line with routine occupational health requirements that healthcare workers have evidence of immunity to specified infectious diseases for which

vaccines are available (for example, MMR, Hepatitis B virus) before they can engage in direct patient care.[104]

There are a number of issues to consider with the use of antibody test results to inform allocation of staff resources. As indicated in Figure 4.1, there is a window during which an individual could have a positive RT-PCR test indicating ongoing acute infection and a positive antibody test indicating an immune response has been mounted. To mitigate the risk of transmission to others, laboratory confirmation of viral clearance (for example, two negative RT-PCR tests at least 24 hours apart) or an adequate time period since RT-PCR confirmation of an acute infection (current guidelines suggest a minimum of 14 days, including five days with no symptoms if applicable) would be required.[94]

For individuals without laboratory-confirmation of acute infection, but for whom SARS-CoV-2 infection was suspected (for example, individuals who did not meet criteria for priority testing or who did not present for testing), again consideration must be given to ensure that sufficient time has elapsed since the presumed exposure and or a requirement for RT-PCR confirmation to exclude acute infection prior to returning to work. False positive test results may incorrectly classify healthcare workers as immune to infection with SARS-CoV-2 placing them at risk of contracting the infection. The specificity of antibody tests for SARS-CoV-2 is an important consideration in circumstances where the test is used to inform staff redeployment. As SARS-CoV-2 has not been previously identified in humans, little is known regarding the adequacy of the immune response or the duration of immunity following seroconversion. Therefore, it is not known if reinfection can occur. As with the influenza virus, there is potential for antigenic drift and thus the potential that immunity is limited to the initial strain of the virus.

From an operational perspective, consideration for the deployment and governance of such an approach should include details of who is responsible for:

- providing the antibody test and in what setting it will be provided
- decision-making in relation to staff redeployment
- follow-up of the individual to ensure immunity in the context of an ongoing pandemic or evidence of the emergence of new strains of the virus.

How, where and by whom any testing to inform staff redeployment is implemented could also have important implications for how the veracity of an individual's test result is ensured given the financial imperative for many individuals to return to work.

Population-level seroepidemiological studies to inform public health strategies

Well-constructed seroepidemiological studies could provide important information on:

- age-specific and cumulative incidence rates of infection
- prevalence of cross-reactive antibodies to SARS-CoV-2
- the clinical spectrum of the infection including the correlation between infection, disease and the detection of antibodies
- evidence of human-to-human transmission to identify, for example, evidence of household and occupational risk of transmission and acquisition.

Seroprevalence studies could be used to determine the level of immunity in the population and may provide a useful indicator of the risk of a second surge in cases after social distancing measures are lifted.[97] Studies to estimate the level of immunity to the virus may be carried out after a consistent decline in the number of cases identified has been observed in order to inform the safe and timely lifting of social distancing restrictions. Such studies can also facilitate evaluation of the effectiveness of any measures introduced to prevent viral transmission (for example, social distancing, school closures) and the requirement to continue such measures.

The use of population-level seroprevalence studies to inform a public health response is well documented in the context of other respiratory pathogens including the Middle East respiratory syndrome (MERS) coronavirus and the 2009 influenza pandemic.[105, 106]

Population level seroepidemiological studies are resource intensive. Interpretation of the findings is critically dependent on a wide range of factors including the demographics of the population tested, the specificity of the test used and issues relating to the sample type and handling. Any decision to implement population-level testing should therefore only be undertaken in the context of a well-designed research study with appropriate governance and controls.

5. Diagnostic tests approved for use internationally

Key points

- An increasing number of diagnostic tests have been approved or authorised for use internationally to address the growing spread of COVID-19.
- To facilitate increased access to diagnostic tests, many international regulatory authorities have established accelerated regulatory pathways in relation to the development of in-vitro diagnostics.
- The Food and Drug Administration (FDA) issued 'immediately in effect guidance' that permits the development and distribution by commercial manufacturers, or development and use by laboratories, of serology tests to identify antibodies to SARS-CoV-2, provided the test has been validated and notification has been provided to the FDA.
- The Health Products Regulatory Authority (HPRA) in Ireland has developed a regulatory derogation process for the urgent assessment of applications to use critical non-CE marked medical devices to address the COVID-19 emergency nationally.
- To date, the tests that have been approved or authorised for use internationally largely include molecular tests and immunoassay tests.

5.1 Introduction

An increasing number of diagnostic tests have been approved or authorised for use internationally to address the growing spread of COVID-19. The scale of the pandemic has resulted in regulatory authorities in many countries establishing accelerated regulatory pathways in relation to the development of in-vitro diagnostics to facilitate access to critical tests. This section presents a brief overview of the regulatory processes that have been introduced for the development and use of diagnostic tests in a number of different countries, including the US, South Korea, Singapore, Australia, Canada, and Ireland, and provides a list of the tests that have been approved or authorised for use in these settings.

5.2 An overview of the international regulatory processes

On 4 February 2020, the FDA in the US moved from approving diagnostic tests to authorising their use through emergency use authorizations (EUAs).[(107)] On 29 February 2020, it subsequently issued an 'immediately in effect guidance' that

permitted the development and distribution by commercial manufacturers, or development and use by laboratories, of serology tests to identify antibodies to SARS-CoV-2, provided the test had been validated and notification was provided to the FDA of its commercial use.[107]

In South Korea, a number of diagnostic tests have been made available for commercial use through the same EUA as in the US[108] since 4 February 2020.[109] In Singapore, on 29 January 2020, the Health Sciences Authority (HAS) granted provisional authorisation for a number of diagnostic tests to be used commercially to ensure the timely availability of good quality tests.[110] In Australia, the Therapeutic Goods Administration (TGA) is undertaking an expedited assessment of all medical devices associated with the detection of COVID-19 and has already approved a number of tests for use under the Australian Register of Therapeutic Goods (ARTG).[111] The Minister for Health in Canada approved an interim order on 18 March 2020 to expedite the review of medical devices, including test kits, for the detection of COVID-19.[112] Priority is being given to diagnostic tests that use nucleic acid technology (molecular tests) in Canada.

In Europe, diagnostic tests are considered in vitro diagnostic devices which must be CE-marked in accordance with the *In Vitro* Diagnostic Medical Devices Directive (IVDD; 98/79/EC) before being placed on the market. Laboratory-based tests for COVID-19 and near-patient tests (professional use tests) are classified as general category IVDs. Under this directive, manufacturers are required to specify device performance characteristics and for general category IVDs self-declare conformity with the safety and performance characteristics listed in the Directive. Devices intended for self-testing, that is, for use directly by patients, must be assessed by a Notified Body for the self-testing aspects.

A number of test for COVID-19 are now CE-marked. In Ireland, the HPRA is the Competent Authority for medical devices and IVDs, and monitors the safety of medical devices and IVDs after they are placed on the market. The HPRA has also developed a national regulatory derogation process for the urgent assessment of applications to facilitate the use of critical non-CE marked medical devices and IVDs in the context of the COVID-19 emergency in Ireland.[113]

5.3 Tests approved or authorised for use internationally

A list of the diagnostic tests reported to have been approved or authorised for use in different regions is provided in Appendix A. To date, these largely comprise molecular tests and immunoassays. The molecular tests are aimed at pathogen detection and are typically PCR-based tests intended for use in laboratory settings by skilled technologists, although some are designed as near-patient testing devices that can be used in non-laboratory settings and require minimal training. One

antigen test is also listed in Appendix A, Table A.1, as CE-marked; antigen tests are aimed at pathogen detection and are therefore intended to identify active infection. The immunoassay tests predominantly comprise rapid antibody tests. These detect the body's immune response to an infection and are helpful in determining a history of infection rather than active infection.

The list of approved or authorised tests for use in Australia, Canada, Singapore, South Korea, and the US detailed in Appendix A is accurate as of 14 April 2020. The list of tests for which CE-marking is claimed is accurate as of 27 March 2020; however, the list is not exhaustive as there is no centralised list of verified CE-marked tests. The list was compiled from a review of various grey literature sources, as detailed in Section 6. Many more diagnostic tests may conform to the relevant EU legislation for CE markings, but may not be available to purchase in Europe as they may be intended for third-country markets, for example.[36] The ECDC report that more than 60 antibody tests have been CE-marked to date, along with 10 antigen tests (1 April 2020). However, according to authorities in 18 European countries, only three antigen tests were CE-marked, as of 26 March 2020.[36]

5.4 Discussion

Many international regulatory authorities have established accelerated regulatory pathways in relation to the development and use of diagnostic tests to facilitate increased access to diagnostic tests during the COVID-19 pandemic. The majority of the tests that have been approved or authorised for use largely include molecular tests and immunoassay tests, which predominantly comprise rapid antibody tests. As yet, none of the rapid antibody tests have been independently validated meaning the clinical performance of these tests remains uncertain. The next section presents an overview of the performance characteristics of alternative diagnostic testing approaches, in particular rapid diagnostic testing approaches.

6. Performance characteristics

Key points

- This section comprises a review of the characteristics of IVD tests for COVID-19 claiming CE-marking. Due to time constraints, the claimed CE-marking was not verified with relevant authorities. Its purpose is to illustrate the number and range of IVDs commercialised for COVID-19.
- Prior to their introduction as standalone diagnostic tests, it is considered best practice to perform clinical validation of the performance of test kits compared with an existing validated protocol for the gold-standard test. The evidence presented in this section is primarily from manufacturer sites and therefore independent validation of the data reported is still required.
- Preliminary evidence of independent validation of diagnostic assays for detection of SARS-CoV-2 is beginning to emerge in the published literature, but none of these studies have yet been peer-reviewed. In addition to independent validation, local verification of test performance should be undertaken in the setting in which use of the test is intended. All diagnostic testing should be undertaken in the context of an ongoing quality assurance programme to ensure confidence in the test results for both the physician and the patient.
- Seventeen CE-marked laboratory-based RT-PCR tests, all of which used nucleic acid amplification technology (NAAT), were identified. Only six of the manufacturers reported clinical sensitivity and specificity, ranging from 96%-100% and 94%-100%, respectively.
- Thirteen CE-marked antibody (including laboratory-based and rapid assays) tests for detection of antibodies to SARS-CoV-2 were identified, all of which use immunoassay technology. Clinical sensitivity and specificity was reported by eight manufacturers, ranging from 85-100% and 91-100%, respectively. However, the reference standard used for comparison of diagnostic performance was only reported by three of the manufacturers. Analytical sensitivity (limit of detection) and specificity (cross-reactivity) was reported by only one manufacturer.
- Two other CE-marked tests for diagnosis of COVID-19 were identified – an antigen rapid assay and a microfluidic chip. Sensitivity and specificity were not reported by the manufacturers.

- Prior to their introduction as standalone diagnostic tests, it is considered best practice to perform clinical validation of the diagnostic performance of test kits compared with an existing validated protocol for the gold-standard test.
- Manufacturer innovation has led to the development of near-patient tests for SARS-CoV-2 antibody detection. However, the implementation of these tests in non-laboratory healthcare settings would need to be accompanied by a quality assurance programme to mitigate against any potential health and safety risks, in accordance with criteria set out by the HSE's National Clinical Programme for Pathology.

6.1 Introduction

This section provides an overview of the performance characteristics of alternative diagnostic testing approaches. These include:

- sensitivity and specificity
- test turnaround time
- organisational and infrastructural requirements.

6.2 Methods

Diagnostic test accuracy

Diagnostic test accuracy (DTA) of tests designed to detect SARS-CoV-2 reflects how well the test discriminates between those who do, and do not have COVID-19. To determine the DTA of an index test, its performance must be compared with that of a 'gold standard' diagnostic test (that is, the best available method for determining the presence of disease) in terms of sensitivity and specificity.

Sensitivity is the ability of an index test to accurately identify those who have the condition: the proportion of people with the condition who receive a positive test result. The specificity of a screening test is its ability to correctly identify those who do not have the condition: the proportion of people without the condition who receive a negative test result. In order to calculate sensitivity and specificity, individuals are classified according to whether the screening test is positive or negative, and whether the 'gold standard' is positive (disease present) or negative (disease absent) – see Table 6.1.

Table 6.1. Relationship between a screening test result and the occurrence of the condition

Test result	Condition present*	Condition absent*
Positive	True positive (a)	False positive (b)
Negative	False negative (c)	True negative (d)

* As determined by the gold standard diagnostic test
Sensitivity is calculated as a/(a+c). Specificity is calculated as d/(b+d).

Information sources

A list of test devices for detection of SARS-CoV-2 was compiled through review of data from a variety of grey literature sources:

- Report on COVID-19 diagnostics by Saw Swee Hock School of Public Health (Singapore, dated March 19 2020).
- Online repositories of available manufacturer diagnostic tests (for example, FIND, 360Dx and Rapidmicrobiology) up to 1 April 2020.[114-117]
- Data obtained from manufacturer websites and technical documentation.

Only devices where the manufacturer claims of Conformité Européenne (CE) marking for an in-vitro diagnostic (IVD) featured in accompanying material on their website are included in this section. Where an accompanying manuscript submitted for publication was identified, these data were included. Of note also, there is no centralised list of verified CE-marked tests. Given the time constraints for this review, it was not possibly to contact all relevant authorities to confirm registration of the tests by the manufacturer or their authorised representative, so it is possible that the list includes IVDs that do not meet the requirements for CE-marking.

A systematic search was conducted up to 27 March 2020 in accordance with the HIQA protocol for evidence synthesis to support SARS-CoV-2 public health response in Ireland to supplement the manufacturer-specific data.

While a systematic review of the literature is routinely used in HTA to assess diagnostic test accuracy, this approach was not adopted in this rapid assessment as such a review was considered premature at the time this assessment was undertaken. SARS-CoV-2 is a novel pathogen in humans first detected in December 2019. A full systematic review would require the definition of clear review questions (for example, using the population, intervention, comparator, outcomes, study design (PICOS) framework) and quality appraisal. Literature published in the first four months of the year (January to April 2020) are primarily in the form of case reports and case series. The majority of the publications have not as yet been peer-reviewed. The findings of the studies should therefore be interpreted with caution

and will require confirmation using larger more robust study designs. As evidence of a non-peer-reviewed variety is rapidly emerging, the data presented in this section focuses on that identified from grey literature sources and that reported by manufacturers as an illustration of the number and range of devices being brought to the market.

Data quality

The tests included in this section are considered as in-vitro diagnostic medical devices and are identified by the respective manufacturers as CE-marked in accordance with the IVD Directive (98/79/EC) under which they are classified as general category IVDs. Under this directive, manufacturers are required to specify device performance characteristics and self-declare conformity with the safety and performance characteristics listed in the Directive. It is noted that the performance of both laboratory-based tests and near-patient testing devices may differ to that reported by manufacturers for the purposes of CE-marking. Prior to their introduction as standalone diagnostic tests, clinical validation of the diagnostic performance compared with a gold-standard would be considered best practice.

The performance data collated in this section of the report may be subject to bias as they are limited to the manufacturer-reported characteristics. Prior to their introduction as standalone diagnostic tests, test kits require independent validation and verification for use at a local level. Clinical validation of the diagnostic performance of the test kit should be compared with an existing validated protocol for the gold-standard, but may be conducted on the basis of a truncated validation run involving fewer samples, with risk mitigated by enhanced surveillance of test performance, given the current requirement for rapid deployment.

None of the included manuscripts was peer-reviewed (as of 2 April 2020) and quality appraisal was beyond the scope of the current rapid HTA. In general, clinical data were presented either in a summary table (as per Table 4.1) without adequate description of methods undertaken in the clinical study or as standalone point estimates of DTA without any description at all. All of the extracted data were checked by a second reviewer.

Data analysis

Where manufacturers reported sufficient data to compile two-by-two tables (to determine the number of true positives, false negatives, true negatives and false positives), mean values and imprecision (that is, 95% confidence intervals) were estimated for sensitivity and specificity using the *metaprop* command in the *meta* package of RStudio version 3.6.3. Subgroup analysis, where appropriate, was performed on these data only (that is, devices were excluded from subgroup analysis where insufficient data were reported) and presented in forest plots. A summary pooled estimate of DTA was not undertaken.

6.3 Findings

The findings are presented according to the following headings:

- RT-PCR tests
- Antibody tests
- Other tests (antigen and microfluidic chip).

As described in Section 4, these test types have clinical utility during different periods within the clinical pathway. Therefore, they should not be viewed as competing alternatives.

RT-PCR

The initial identification of SARS-CoV-2 was based on non-commercial laboratory protocols which were published on the WHO website. The initial testing protocols, include multiple steps involving manual manipulation and take six to seven hours to complete. However, RT-PCR is not a new technology; it is widely used in specialised laboratories testing for viral testing. Therefore companies have developed and commercialised RT-PCR test kits, many of which work off existing platforms already deployed in Irish hospital and testing laboratories.

As noted, prior to their introduction as standalone diagnostic tests, best practice is for independent clinical validation of the diagnostic performance of the test kit compared with an existing validated protocol for the gold-standard as well as local level verification in the setting in which the test will be used. Given the current requirement for rapid deployment, this may be on the basis of a truncated validation run involving fewer samples, with risk mitigated by enhanced surveillance of test performance.

Some of the test kits can be used in platforms with a higher degree of automation, requiring less manual manipulation, less reagent and that are amenable to batch testing, thereby facilitating shorter turnaround times and a higher throughput of tests. Advantages of test kits suitable for use on existing platforms include that the platforms are already deployed in a number of the hospital laboratories, and there is a level of multidisciplinary experience and confidence in their use

As described in Section 4, the performance of RT-PCR is instrument-dependent, and influenced by the reaction components and conditions. Rapid PCR test kits with optimised target regions and primer sequences increase the speed and convenience of PCR to support timely and accurate diagnosis, but upscaling of testing with the use of rapid PCR kits must leverage from existing laboratory resources to optimise the expansion of testing. Optimised throughput and diagnostic performance of the PCR test kits presented in this section rely on the availability of reagents, primer sequences and automated systems.

In total, 17 laboratory-based RT-PCR tests were identified for inclusion, all of which use nucleic-acid amplification technology (NAAT).[118-134] Overall, 12 manufacturers reported the technology's sample type on their website. These mainly comprised samples of the lower and upper respiratory tract such as bronchoalveolar lavage fluid, nasopharyngeal and oropharyngeal swabs, and sputum. Test capacity, run time and additional laboratory materials (beyond that of the test kit) required were reported by six, 11 and six of the manufacturers, respectively. Throughput was reported by two manufacturers according to their manufacturer-specific automated systems.[128, 132] Primerdesign Ltd reported that their Cobas® SARS-CoV-2 (Real-Time PCR assay) could deliver 384 and 1,056 results in eight hours using the Cobas® 6800 System and Cobas® 8800 System, respectively.

Device performance was reported both analytically and clinically. Clinical sensitivity and specificity was reported by five of the device manufacturers.[121, 123, 124, 128, 132] Of these, four manufacturers reported the underlying clinical data.[120, 121, 128, 132] One manufacturer reported clinical diagnostic data for lower and upper respiratory tract samples (compared with the CDC's FDA-EUA 2019-Novel Coronavirus (2019-nCoV) Real-time RT-PCR Panel).[132] The comparator was not reported by the other manufacturers. Across all of these data (n=5), clinical sensitivity ranged from 89% to 100%, and clinical specificity ranged from 94% to 100%. For some tests,[121, 128] measures of diagnostic test accuracy were based on non-clinical performance evaluation whereby samples from healthy individuals were spiked with viral targets prior to RNA extraction and subsequent performance evaluation.

Analytical sensitivity (limit of detection) was reported by nine manufacturers (Appendix B, Table B1). Six manufacturers reported that there was no cross-reactivity with other viral infections, such as influenza (but the assessment of cross-reactivity varied by manufacturer).[120, 121, 127, 131, 132, 134] The others did not comment on the potential for cross-reactivity. Estimates of cross-reactivity are dependent on the pathogens included in the assessment. Not all manufacturers investigated cross-reactivity with other coronaviruses known to demonstrate a high degree of sequence similarity. Manufacturer-specific data are presented in (Appendix B, Tables B1 and B2).

Given that these data have been self-reported by the manufacturers, they should be interpreted with caution, and require validation and verification prior to establishment of standardised local use. A study evaluating the performance of four manufacturer-claimed CE-marked NAATs widely used in China during the pandemic found that the analytical sensitivity of the four assays was significantly lower than that claimed by the NAAT manufacturers.[135] The clinical sensitivity of one of the assays was also significantly reduced compared with that reported by the

manufacturer. Clinical sensitivity may also vary according to primer-probe sets used during RNA extraction.[136]

Antibody tests

As described in Section 4, it has been suggested that antibody tests may present operational utility in particular circumstances later in the disease course (following seroconversion), such as in decision-making regarding return to work for healthcare workers. There has been considerable focus in manufacturer innovation on the development of near-patient testing devices for SARS-CoV-2 antibody detection. As testing is currently laboratory-based, the implementation of near-patient testing in other healthcare settings would need to be accompanied by a quality assurance programme to mitigate against any potential health and safety risks, in accordance with criteria set out by the HSE's National Clinical Programme for Pathology. Therefore, the findings reported below should be interpreted in the context of an accompanying quality assurance programme.

In total, 13 antibody (including laboratory-based and rapid assays) tests for detection of the SARS-CoV-2 antibody were identified, all of which use immunoassay technology.[137-149] All of the manufacturers reported the technology's sample type on their website comprising whole blood, serum and plasma. Sample capacity was reported by eight manufacturers (one unit in each case). Runtime was reported by 11 manufacturers ranging from 2-30 minutes. Additional testing materials (beyond that of the test kit) required was reported by three manufacturers – one manufacturer stated that no additional materials or equipment were required.[147]

The comparator for estimation of clinical sensitivity and specificity was reported by three manufacturers, being one of or a combination of RT-PCR, clinical diagnosis or single IgG/IgM detection (for comparison with dual detection).[138, 140, 146] Clinical sensitivity and specificity was reported by eight manufacturers.[137, 138, 140, 141, 144-146, 149] Of these, five manufacturers reported the underlying clinical data.[137, 138, 140, 146, 149] Across all of these data (n=8), clinical sensitivity ranged from 85% to 100%, and clinical specificity ranged from 96% to 100%. However, these ranges should be interpreted with caution given that the reference standard used for comparison was not reported by 10 of the manufacturers. The data from one manufacturer has been included as part of a manuscript submitted for peer-review publication.[140, 150] A manuscript reporting the evaluation of nine commercial antibody tests undertaken by the Danish national state laboratory was also identified. The performance data for three immunoassays evaluated in the study were included in this section.[141-143, 151]

Sufficient data were provided by four manufacturers to enable subgroup analysis according to single IgG or single IgM detection.[137, 138, 146, 149] In antibody tests for single IgG detection, clinical sensitivity ranged from 97% to 100% and clinical

specificity ranged from 98% to 100%. In antibody tests for single IgM detection, clinical sensitivity ranged from 88% to 94% and clinical specificity ranged from 96% to 100%.

Analytical sensitivity (limit of detection) was reported by only one manufacturer at 3.4 ng/mL and 210 ng/mL for IgG and IgM, respectively.[146] Only one manufacturer reported no cross-reactivity with human influenza A and B viruses, anti-respiratory syncytial virus, anti-adenovirus, hepatitis B virus antigen, anti-Treponema pallidum, anti-helicobactor pylori, anti-human immunodeficiency virus, and anti-hepatitis C virus.[149] The others did not comment on the potential for cross-reactivity. Manufacturer-specific data are presented in (Appendix B, Tables B3 and B4) and in forest plots in Appendix B (Figures B1-B3).

Other tests (antigen and microfluidic chips)

Two other manufacturer-claimed CE-marked tests for diagnosis of COVID-19 were identified – an antigen rapid assay and a microfluidic chip.[152, 153] Turnaround for these tests was 10 minutes for the antigen test and 40 minutes for the microfluidic chip. Sensitivity and specificity were not reported by the manufacturers. Further details of these tests are presented in Appendix B, Table B5.

7. Discussion

The assessment was undertaken as a rapid assessment within very restricted timelines and in the context of a global pandemic of a new pathogen in humans. It therefore differs from a standard health technology assessment in its scope and the approaches adopted to synthesising the available evidence.

In particular, while a systematic review of the literature is routinely used in HTA to assess diagnostic test accuracy, this approach was not adopted in this rapid assessment as such a review was considered premature. SARS-CoV-2 is a novel pathogen in humans first detected in December 2019. Literature published in the first four months of this year are primarily in the form of case reports and case series; the majority of the publications have not as yet undergone peer-review. The findings of the studies should therefore be interpreted with caution and will require confirmation using larger more robust study designs.

This preliminary review is therefore limited to manufacturer-reported evidence for the performance characteristics of tests they claim are CE-marked. It therefore may be subject to bias. As noted in Section 6, prior to their introduction as standalone diagnostic tests, test kits require independent validation and verification for use at a local level.

Pre-analytical vulnerabilities, independent clinical validation and quality assurance

While there has been substantial discussion of the steps necessary to ensure to validate the test accuracy of the individual tests deployed, it must also be highlighted that the pre-analytical phase can be a major source of errors in diagnostic testing. To mitigate such risks, training and quality assurance procedures are required to ensure that test samples are appropriately identified and reported (that is, right result, right patient), and to ensure adequate procedures for correct specimen (for example, swab) collection, handling, transport, and storage.

The results of formal clinical validation studies for commercialised, CE-marked, rapid diagnostic tests funded by the European Commission and EU member states and by WHO referral laboratories are awaited. Until the clinical performance of these tests, in particular rapid diagnostic tests based on antigen detection and host antibody detection, has been validated, the WHO has strongly advised against their use in any setting other than a research setting. Making the distinction between the analytical performance and the clinical performance of diagnostic tests, performance criteria for RT-PCR, antigen-based and antibody-based tests have been published in a working document of the European Commission to provide additional guidance to

the legally obligatory requirements defined in the IVDR to inform research in this area.[68] These criteria are based on the principles of good analytical (testing) practice. The working document notes the current absence of control samples and reference materials as a particular challenge to establishing the diagnostic test accuracy of antigen and antibody tests.[68] The WHO and ECDC have noted that they will update their guidance on the use of diagnostic testing approaches used in laboratories or as near-patient tests in line with the findings from these validation studies. However, the requirement for additional validation studies to confirm that this test performance can be replicated in the context in which they are being used must be emphasised. Given the current requirements for rapid deployment of CE-marked devices, this validation may be conducted on the basis of a truncated validation run involving fewer samples, with risk mitigated by enhanced surveillance of test performance.

While adequate test accuracy and precision may be achieved under idealised circumstances in the laboratory, these may be negatively impacted when used as near-patient tests. Appropriate staff training and use of robust standardised operating procedures may be required to moderate these sources of error. In accordance with existing Irish guidelines for the safe and effective management and use of near-patient (point-of-care) testing, such testing should be performed in the context of an ongoing quality assurance programme to ensure adequate performance of the tests in the context in which they are being used and provide confidence in the test results for both the diagnosing physician and the patient. Consideration should also be given to a requirement that all testing should be ISO-accreditable, including meeting requirements in relation to internal quality control, quality assurance and the recording of training and test results.

Operational utility and potential deployment of different diagnostic testing approaches

The potential operational utility of different molecular and immunological testing approaches was described in detail in Section 4. A clear distinction was drawn between tests that can be used to diagnose acute infection and those that indicate past exposure to the virus.

RT-PCR remains the most sensitive and specific validated method for detection of cases. However, as noted in Section 2.6, negative test results do not preclude SARS-COV-2 infection and cannot be used as the sole basis for patient management decisions. Discrepancies between the analytical performance and the clinical performance of an assay may arise due to pre-analytical issues as highlighted above and due to the impact of differences in viral dynamics over the course of an infection. Specifically, false negative test results may occur if samples are tested

during the early incubation period or during the late convalescent phase, when virus levels may be undetectable. Differences in viral dynamics over the course of an infection may also contribute to discordance between test results based on different specimens (upper versus lower respiratory tract). High test sensitivity is clinically and epidemiologically relevant because asymptomatic and mild cases of COVID-19 have been increasingly recognised. While clinical severity is not always correlated with viral load, asymptomatic and mild cases may have viral loads below the limit of detection of certain tests. The true prevalence of SARS-CoV-2 infection might be underestimated by less sensitive assays. Patients with false negative results may serve as a potential source for propagating the pandemic.

The use of rapid antigen tests to facilitate early diagnosis of acute infection with SARS-CoV-2 to facilitate patient triage and cohorting and or to alleviate pressure on laboratory testing is consistent with approaches adopted in international clinical guidelines for the diagnosis of seasonal influenza. Such guidelines note that where there is access to RT-PCR assays, these are considered the preferred test on the basis of diagnostic test accuracy with the recommendation that antigen detection tests should only be used to rule-in suspected cases. All negative test results should be confirmed by RT-PCR or molecular methods with comparable accuracy.

The role of antibody testing to identify those previously exposed to SARS-CoV-2 was discussed in detail in Section 4. As noted, its operational utility of antibody testing can be considered in the context of three potential scenarios: patient level testing (to inform clinical management); cohort testing to inform staff deployment (for example, immunity passports); and population-level seroepidemiological studies to inform public health strategies.

The use of patient-level testing and population-level seroepidemiological testing are well documented in healthcare. However, the use of antibody testing to inform staff deployment is an unprecedented, but potentially necessary step given the extreme pressures on the healthcare system and the economic ramifications of the current COVID-19 global pandemic. Notwithstanding this, deployment of antibody testing in this context has extremely important implications for both the administration and reporting of tests as well as well as the overall governance of any testing strategy. This is particularly the case given the uncertainty around the potential for re-infection with the same or a different antigenic strain of the SARS-CoV-2 virus. As highlighted in Section 4, prior to deployment, consideration should be given to who will be responsible for:

- providing the antibody test and in what setting will it be provided
- decision-making in relation to the staff redeployment

- follow up of the individual to ensure community immunity in the context of an ongoing pandemic or evidence of the emergence of new strains of the virus.

Furthermore, it is noted that how, where, and by whom any testing to inform staff redeployment is implemented could also have important implications for how the veracity of an individual's test result is ensured given the financial imperative for many individuals to return to work.

Implications of the IVD Regulation (IVDR 2017/746/EU) for IVDs including near-patient testing devices

All IVDs including those for near-patient testing are subject to EU Regulation 2017/746 on In Vitro Diagnostic Devices (the IVDR) which came into force at the end of May 2017. The Regulation has a staggered transitional period, with full application after five years (May 2022). The regulation will replace the existing IVD directive (98/79/EC) and is intended to strengthen the current regulatory system by providing:

- clearer requirements regarding clinical data for IVDs, and their assessment;
- more specific product requirements, such as unique identifiers for IVDs;
- improved pre-market assessment and post-market surveillance of all high-risk devices;
- increased control and monitoring of Notified Bodies by the National Competent Authorities and the Commission;
- more stringent requirements for near-patient tests;
- enhanced traceability for IVDs.

One of the key changes under the IVDR relates to the conformity assessment procedures required of manufacturers prior to an IVD being placed on the market. Requirements vary based on the risk classification of the device, that is, for low risk (Class A) up to high risk (Class D). Assessment and certification by a notified body will be required for those IVDs in Classes B, C, and D. Class A devices placed on the market in a sterile condition shall also require notified body involvement, limited to the sterile aspects of the product. Devices for near-patient testing are classified in their own right under Rule 4(b) of Annex VIII of the IVDR.

Depending on the intended purpose specified by the manufacturer, SARS-CoV-2 near-patient test devices will likely be in Class D. This represents a significant change to the existing regulatory system, where the majority of IVDs are self-declared by the manufacturer rather than being assessed by a notified body.

Detailed requirements for the performance evaluation of IVDs are outlined in the IVDR. The performance evaluation will comprise data on the scientific validity, analytical performance and clinical performance of the device. Under the IVDR, IVDs for near-patient testing must perform appropriately for their intended purpose taking into account the skills of the intended user and the potential variation in the user's technique and environment, with sufficient information provided in order for the user to be able to correctly interpret the result provided. It is recognised that the enhanced regulatory burden arising from implementation of the IVDR may impact the number and range of IVDs on the market.

The Health Products Regulatory Authority (HPRA) is designated as the Competent Authority for medical devices and IVDs in Ireland. Its role is to ensure that all medical devices sold into the Irish market comply with the relevant legislation. This means that a medical device must achieve the performance criteria specified by the manufacturer and in doing so must not compromise the health and safety of patients, service providers and any other persons. In its role as the competent authority, the HPRA operates a vigilance system for medical devices. Vigilance issues include adverse incidents and field safety corrective actions (FSCAs).

8. Conclusions

This assessment was undertaken as a rapid HTA within very restricted timelines and in the context of an evolving global pandemic of a new pathogen in humans. It therefore differs from a standard HTA in its scope and the approaches adopted to synthesising the available evidence. Evidence to support the analytical performance of diagnostic tests for SARS-CoV-2 will continue to emerge. Evidence will also emerge to support the clinical effectiveness and safety of different testing strategies to inform patient care and the public health response to COVID-19. Revisions to any national testing strategy may be required as the evidence evolves. In time, a full HTA that takes consideration of the cost-effectiveness, resource considerations and budget impact of alternative testing strategies may be required to ensure the best outcomes for the resources available.

Bearing in mind the caveats of the approach adopted, and arising from the findings of this report, the following conclusions can be drawn:

- Diagnostic tests for SARS-CoV-2 can be broadly grouped into two categories: those aimed at detecting the virus and those that detect the body's immune response to the infection (past exposure to the virus). These should not be considered competing alternatives; both testing approaches are clinically relevant at different time points during the clinical course of infection.

- The ability of any diagnostic test to achieve an acceptable clinical performance is contingent on it being performed within the appropriate timeframe for the condition in question (right test, right time, right person), with due consideration of the principles of good pre-analytical and analytical testing practice.

- Real-time PCR is the preferred method to detect SARS-CoV-2 RNA and to confirm acute infection early in the clinical course of COVID-19 disease. To increase diagnostic testing capacity, efforts are underway to develop enhanced molecular methods with reduced turnaround times and instrumentation requirements and higher throughput.

- Antigen detection tests could be used to supplement current laboratory-based real-time RT-PCR case detection. However, analytical and clinical validation of these tests is needed to inform their safe and effective use in clinical decision-making.

- Contingent on the availability of accurate, validated tests, antibody tests could be used later in the clinical course of infection or following recovery to identify those who have been exposed to SARS-CoV-2. While the use of antibody tests to provide 'immunity passports' has been proposed in the literature, little is known about the adequacy of the immune response or the duration of immunity, and so it is not known if reinfection can occur. The primary role of antibody tests is likely to be as part of well-constructed seroprevalence studies to model the course of the pandemic and inform the public health response.

- Work is currently underway to validate the analytical performance of the different diagnostic tests. Prior to their introduction as standalone tests, clinical validation studies are also required to confirm that test performance can be replicated in the context in which the test is being used. All testing should be undertaken in the context of an ongoing quality assurance programme to provide confidence in the test results for both the physician and the patient.

- A cohesive national strategy is needed to ensure the right tests are undertaken in the right people at the right time for the right purpose. This is necessary to ensure appropriate governance of SARS-CoV-2 testing and should include clear criteria for the administration and reporting of tests. Planning now to support delivery of the strategy will facilitate rapid deployment of tests that meet the requisite standards once available and validated for use.

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Appendix A – List of internationally approved or authorised SARS-CoV-2 tests

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
Molecular tests							
Abbott Diagnostics Scarborough, Inc.	ID NOW COVID-19						EUA 27/03/2020
Abbott Molecular	Abbott RealTime SARS-CoV-2 assay		Approved (Health Canada) 25/03/2020		Provisional authorisation		EUA 18/03/2020
Acumen Research Laboratories	Acu-Corona™ 2.0				Provisional authorisation		
Acumen Research Laboratories Pte Ltd	Acu-Corona 3.0				Provisional authorisation		
AITbiotech Pte Ltd	abTES™ COVID-19 qPCR I Kit				Provisional authorisation		
Anatolia Geneworks	Bosphore Novel Coronavirus (2019-Ncov) Detection Kit			CE-marked			
Atila BioSystems, Inc.	iAMP COVID-19 Detection Kit						EUA 10/04/2020
AusDiagnostics Pty Ltd (Australia)	AusDiagnostics respiratory virus panel (including SARS-CoV-2) test	TGA approved 19/03/2020					
Avellino Lab USA, Inc.	AvellinoCoV2 test						EUA 25/03/2020
Becton, Dickinson & Company	BD SARS-CoV-2Reagents for BD MAX System						EUA08/04/2020
Becton, Dickinson & Company (BD)	BioGX SARS-CoV-2 Reagents for BD MAX System						EUA 02/04/2020

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
BGI Genomics Co. Ltd	Real-Time Fluorescent RT-PCR Kit for Detecting SARS-2019-nCoV	TGA approved 10/04/2020		CE-marked			EUA 26/03/2020
BioFire Defense, LLC	BioFire COVID-19 Test						EUA 23/03/2020
BioSewoom Inc.	Real-Q 2019-nCoV Detection Kit					EUA	
Centers for Disease Control and Prevention's (CDC)	CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel (CDC)						EUA 04/02/2020
CerTest Biotech (Spain)	VIASURE SARS-CoV-2 Real Time PCR Detection Kit	TGA approved 21/03/2020		CE-marked			
Co-Diagnostics, a US-based molecular diagnostics company	Logix Smart COVID-19 Test (RT-PCR)			CE-marked			EUA 03/04/2020
Credo Diagnostics Biomedical Pte Ltd	VitaPCR™ SARS-CoV-2 Assay				Provisional authorisation		
DiaCarta, Inc	QuantiVirus SARS-CoV-2 Test kit						EUA 08/04/2020
Diagnostic Hybrids, Inc.	LYRA SARS-COV-2 ASSAY		Approved (Health Canada) 25/03/2020				
Diagnostics Development Hub (DxD)	FORTITUDE KIT 2.0				Provisional authorisation		
DiaSorin Molecular LLC	Simplexa COVID-19 Direct assay		Approved (Health Canada) 09/04/2020				EUA 19/03/2020
DSO National Laboratories	Real-Time PCR Assay for the Detection of SARS-CoV-2 Virus				Provisional authorisation		
Genetic Signatures Ltd (Australia)	EasyScreen™ SARS-CoV-2 Detection Kit	TGA approved 13/04/2020					

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
GenMark Diagnostics, Inc.	ePlex SARS-CoV-2 Test						EUA 19/03/2020
Genomica (Spain)	qCOVID-19,			CE-marked			
Genomica (Spain)	CLART COVID-19,			CE-marked			
Gnomegen LLC	Gnomegen COVID-19 RT-Digital PCR Detection Kit						EUA06/04/2020
Hologic, Inc.	Panther Fusion SARS-CoV-2	TGA approved 20/03/2020	Approved (Health Canada) 25/03/2020				EUA 16/03/2020
InBios International, Inc	Smart Detect SARS-CoV-2 rRT-PCR Kit						EUA 07/04/2020
Ipsum Diagnostics, LLC	COV-19 IDx assay						EUA 01/04/2020
JN Medsys Pte Ltd	ProTect™ COVID-19 RT-qPCR Kit				Provisional authorisation		
Kogene Biotech	PowerChek™ 2019-nCoV Real-time PCR Kit			CE-marked		EUA	
Laboratory Corporation of America (LabCorp)	COVID-19 RT-PCR Test						EUA 16/03/2020
Liferiver Bio-Tech	Novel Coronavirus (2019-nCoV) Real Time Multiplex RT-PCR kit Detection for 3 genes			CE-marked			
Luminarie Canada Inc.	1COPY COVID-19 QPCR KIT		Approved (Health Canada) 03/03/2020				
Luminex Corporation	ARIES SARS-CoV-2 Assay						EUA 03/04/2020

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
Luminex Molecular Diagnostics, Inc.	NxTAG CoV Extended Panel Assay		Approved (Health Canada) 26/03/2020				EUA 27/03/2020
Mesa Biotech Inc.	Accula SARS-Cov-2 Test						EUA 23/03/2020
MiRXES Pte Ltd	MiRXES FORTITUDE KIT 2.0				Provisional authorisation		
NeuMoDx Molecular, Inc.	NeuMoDx SARS-CoV-2 Assay						EUA 30/03/2020
OSANGHealthcare Korea	GeneFinderTM COVID-19 Plus RealAmp Kit			CE-marked			
PerkinElmer, Inc.	PerkinElmer New Coronavirus Nucleic Acid Detection Kit		Approved (Health Canada) 06/04/2020				EUA 24/03/2020
Primerdesign Ltd.	COVID-19 genesig Real-Time PCR assay			CE-marked			EUA 20/03/2020
QIAGEN GmbH	QIAstat-Dx Respiratory SARS-CoV-2 Panel						EUA 30/03/2020
Quest Diagnostics Infectious Disease, Inc.	Quest SARS-CoV-2 rRT-PCR						EUA 17/03/2020
Quidel Corporation	Lyra SARS-CoV-2 Assay						EUA 17/03/2020
Roche Molecular Systems, Inc. (RMS)	cobas SARS-CoV-2	TGA approved 20/03/2020	Approved (Health Canada) 18/03/2020	CE-marked	Provisional authorisation		EUA 12/03/2020
Sansure	Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (PCR-Fluorescence Probing			CE-marked			
ScienCell Research Laboratories	ScienCell SARS-CoV-2 Coronavirus Real-time RT-PCR (RT-qPCR) Detection Kit						EUA 03/04/2020
SD Biosensor	STANDARD M n-CoV Real-Time Detection Kit for emergency COVID-19 test			CE-marked		EUA	

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
Seegene Inc (Korea) / All Eights (Singapore)	Allplex™ 2019-nCoV Assay	TGA approved 27/03/2020	Approved (Health Canada) 09/04/2020	CE-marked	Provisional authorisation	EUA	
Solgent	DiaPlexQ™ Novel Coronavirus (2019-nCoV) Detection Kit		Approved (Health Canada) 05/04/2020	CE-marked		EUA	
Spartan Bioscience Inc. (Canada)	Spartan Cube CYP2C19 System		Approved (Health Canada) 11/04/2020				
SPD Scientific Pte Ltd / Cepheid	Cepheid® Xpert® Xpress SARS-CoV-2	TGA approved 22/03/2020	Approved (Health Canada) 24/03/2020		Provisional authorisation		EUA 20/03/2020
Thermo Fisher Scientific, Inc.	TaqPath COVID-19 Combo Kit	TGA approved 24/03/2020	Approved (Health Canada) 18/03/2020		Provisional authorisation		EUA 13/03/2020
Trenton Biomedical Ltd (Credo Diagnostics.)	VitaPCR COVID-19 assay			CE-marked			
Vircell	SARS-CoV-2 RealTime PCR kit			CE-marked			
Wadsworth Center, New York State Department of Public Health's (CDC)	New York SARS-CoV-2 Real-time Reverse Transcriptase (RT)-PCR Diagnostic Panel						EUA 29/02/2020
Serology/immunoassay tests							
Acro Biotech Inc (USA)	Assay Genie COVID-19 Rapid POC (Point-of-Care) kit			CE-marked			
Alfa Scientific Designs, Inc.	Instant-view plus COVID-19 IgG/IgM Antibody Test						FDA notified
Alfa Scientific Designs, Inc.	Clarity COVID-19 IgG/IgM Antibody Test						FDA notified
Assure Tech (Hangzhou) Co., Ltd.	COVID-19 IgG/IgM Rapid Test Device						FDA notified

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
Atlas Link (Beijing)Technology Co., Ltd	NovaTest: One Step COVID-19 IgG/IgM rapid test						FDA notified
Autobio Diagnostics	Anti-SARS-CoV-2 Rapid Test						FDA notified
Aytu BioScience (China)	COVID-19 IgG/IgM Rapid Test			CE-marked			
Beijing Beier Bioengineering Co., Ltd	2019-New Coronavirus IgG/IgM Rapid Test Cassette (WB/S/P)						FDA notified
Beijing Decombio Biotechnology Co., Ltd.	Novel Coronavirus IgM/IgG Combo Rapid Test-Cassette (Serum/Plasma/Whole blood)						FDA notified
Beijing Diagreat Biotechnologies Co., Ltd.	2019-nCoV IgG Antibody Determination Kit						FDA notified
Beijing Diagreat Biotechnologies Co., Ltd.	2019-nCoV IgM Antibody Determination Kit						FDA notified
Beijing Diagreat Biotechnologies Co., Ltd.	2019-nCoV IgG/IgM Antibody Rapid Test Kit						FDA notified
Beijing Kewei Clinical Diagnostic Reagent Inc.	Genonto RapidTest10 COVID-19 IgG/IgM Antibody Rapid Test Kit						FDA notified
Beijing O&D BIOTECH Co., LTD.	Coronavirus disease(COVID-19) Total Antibody Rapid Test (Colloidal Gold)						FDA notified
Beijing Wantai Biologicalpharmacy Enterprise Co Ltd (China)	Wantai SARS-CoV-2 Ab Rapid Test kit	TGA approved 27/03/2020					FDA notified
Beroni Group	SARS-CoV-2 IgG/IgM Antibody Detection Kit						FDA notified
Bioeasy (USA)	2019-NOVEL CORONAVIRUS (2019-nCoV) IgG/IgM GICA RAPID TEST KIT			CE-marked			
Biohit Healthcare (Hefei) Co., Ltd.	SARS-CoV-2 IgM/IgG antibody test kit (Colloidal Gold Method)						FDA notified
Biolidics Limited	Nanjing Vazyme/Biolidics 2019-nCoV IgG/IgM Detection Kit				Provisional authorisation		FDA notified
BioMedomics, Inc.	COVID-19 IgM-IgG Rapid Test			CE-marked			FDA notified
BioSys Laboratories, Inc.	BioSys Plus COVID-19 IgM/IgG Rapid Test						FDA notified
BTNX, Inc. Rapid Response™	COVID-19 IgG/IgM Test Cassette						FDA notified

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
Camtech Diagnostics Pte Ltd	Camtech COVID-19 IgM/IgG				Provisional authorisation		
Cellex Inc (United States Of America)	Cellex qSARS-CoV-2 IgG/IgM Cassette Rapid Test kit	TGA approved 31/03/2020					
Chembio Diagnostic Systems, Inc.	DPP COVID-19 IgM/IgG System						FDA notified
Core Technology Co., Ltd.	CoreTest COVID-19 IgM/IgG Ab Test						FDA notified
Core Technology Co., Ltd.	RapidTest COVID-19 IgM/IgG Ab Test						FDA notified
Coronacide™	COVID-19 IgM/IgG Rapid Test						FDA notified
CTK Biotech	CTK Biotech, Inc., OnSite COVID-19 IgG/IgM Rapid Test	TGA approved 19/03/2020		CE-marked			FDA notified
DIALAB(ZJG) Biotech Co., Ltd.	SARS-CoV-2 IgG/IgM Antibody Test (Fluorescence Immunoassay)						FDA notified
Diazyme Laboratories, Inc.	Diazyme DZ-LITE SARS-CoV-2 IgG CLIA Kit						FDA notified
Diazyme Laboratories, Inc.	Diazyme DZ-Lite SARS-Cov-2 IgM CLIA Kit						FDA notified
Diazyme Laboratories, Inc.	Diazyme SARS-CoV-2 Antibody Rapid Test						FDA notified
Dynamiker Biotechnology (Tianjin) Co. Ltd, China,	Dynamiker Biotechnology (Tianjin) Co., Ltd., 2019 nCOV IgG/IgM Rapid Test			CE-marked			
Eachy Biopharmaceuticals Co., Ltd.	AccuRapid™ SARS-CoV-2 IgM/IgG Test Kit (Lateral Flow Immunoassay)						FDA notified
Eachy Biopharmaceuticals Co., Ltd.	SmartScreen COVID-19 IgM/IgG Test Kit						FDA notified

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
EpiGentek	SeroFlash SARS-CoV-2 IgM/IgG Antibody Detection Kit						FDA notified
Epitope Diagnostics, Inc.	KT-1032 EDI™ Novel Coronavirus COVID-19 IgG ELISA Kit						FDA notified
Epitope Diagnostics, Inc.	KT-1033 EDI™ Novel Coronavirus COVID-19 IgM ELISA Kit						FDA notified
ET Healthcare Inc.	Pylon COVID-19 IgM/IgG Assay						FDA notified
EUROIMMUN AG	Anti-SARS-CoV-2 ELISA (IgA)						FDA notified
EUROIMMUN AG	Anti-SARS-CoV-2 ELISA (IgG)						FDA notified
EUROIMMUN AG	ELISA assay for detection of Anti SARS-COV-2: IgA, IgG			CE-marked			
Everest Links Pte Ltd / VivaChek Biotech (Hangzhou) Co., Ltd.	VivaDiag™ COVID-19 IgM/IgG Rapid Test	TGA approved 26/03/2020			Provisional authorisation		FDA notified
GenBody Inc.	GenBody COVID-19 IgM/IgG						FDA notified
Genrui Biotech Inc.	Novel Coronavirus (2019-nCoV) IgG/IgM Test Kit (Colloidal Gold)						FDA notified
Getein Biotech Inc.	One Step Test for Novel Coronavirus (2019-nCoV) IgM/IgG antibody (Colloidal Gold)						FDA notified
Goldsite Diagnostics Inc	SARS-CoV-2 IgG/IgM ki						FDA notified
Guangzhou Fenghua Bioengineering Co., Ltd.	SARS-CoV-2 IgG/IgM Rapid Testt						FDA notified
Guangzhou Wondfo Biotech Co., Ltd. / SkyQuest Pte Ltd.	SARS-CoV-2 Antibody Test	TGA approved 25/03/2020			Provisional authorisation		FDA notified
Hangzhou AllTest Biotech Co., Ltd.	AllTest 2019-nCoV IgG/IgM Rapid Test Cassette						FDA notified
Hangzhou AllTest Biotech Co., Ltd.	AllTest COVID IgG/IgM Rapid Test Dipstick						FDA notified
Hangzhou Biotest Biotech	COVID-19 IgG/IgM Rapid Test Cassette	TGA approved 23/03/2020					FDA notified
Hangzhou Clongene Biotech Co., Ltd. Clungene	COVID-19 IgM/IgG Rapid Test Cassette	TGA approved 26/03/2020					FDA notified

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
Hangzhou Laihe Biotech Co Ltd (China)	Novel Coronavirus (2019-nCoV) IgM/IgG Antibody Combo Test Kit (Colloidal Gold)	TGA approved 06/04/2020					
Hangzhou Realy Tech Co Ltd.	2019-nCOV IgG/IgM Rapid Test						FDA notified
Hangzhou Testsealabs Biotecnology Co.	One Step SARS-CoV2 (COVID-19) IgG/IgM Test						FDA notified
Healgen Scientific, LLC.	COVID-19 IgG/IgM Rapid Test Cassette(Whole Blood/Serum/Plasma)						FDA notified
INNOVITA (Tangshan) Biological Technology Co., Ltd.	2019-nCoV Ab Test (Colloidal Gold)	TGA approved 04/04/2020					FDA notified
InTec Products,	Rapid SARS-CoV-2 Antibody Test			CE-marked			
InTec Products,	Rapid SARS-CoV-2 Antibody (IgM/IgG) Test			CE-marked			
Jiangsu Dablood Pharmaceutical Co, Ltd.	AssuranceAB™ COVID-19 IgM/IgG Rapid Antibody Test						FDA notified
Jiangsu Dablood Pharmaceutical Co. Ltd.	COVID-19 IgM/IgG Rapid Test						FDA notified
Jiangsu Macro & Micro-Test Med-Tech Co., Ltd.	SARS-CoV-2 IgM/IgG Rapid Assay Kit (Colloidal Gold)						FDA notified
Lifeassay Diagnostics (Pty) Ltd	Test-it COVID-19 IgM/IgG Lateral Flow Assay						FDA notified
Liming BioProducts Co. Ltd.	SARS-CoV-2 IgM/IgG Antibody Rapid Test						FDA notified
Maccura Biotechnology Co., Ltd.	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) IgM/IgG Antibody Assay Kit by Colloidal Gold Method						FDA notified
Medical Systems Biotechnology Co., Ltd.	Coronavirus Disease 2019 Antibody (IgM/IgG) Combined Test Kit						FDA notified
Mokobio Biotechnology R&D Center	SARS-CoV-2 IgM & IgG Quantum Dot Immunoassay						FDA notified
nal von mindenGmbH	Nadal COVID-19 IgG/IgM Test (test cassette)			CE-marked			
Nanjing Liming Bio-products Co.,Ltd	SARS-CoV-2 IgM/IgG Antibody Rapid Test Kit						FDA notified
NanoResearch, Inc. NanoMedicina™	SARS-COV-2 IgM/IgG Antibody Rapid Test						FDA notified

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
Nantong Diagnos Biotechnology Co., Ltd.	(2019-nCoV) New coronavirus Antibody Test (Colloidal Gold)						FDA notified
Nirmidas Biotech, Inc.	COVID-19 (SARS-CoV-2) IgM/IgG Antibody Detection Kit						FDA notified
PCL Inc.	COVID19 IgG/IgM Rapid Gold						FDA notified
Phamatech Inc.	COVID19 IgG/IgM Rapid Test						FDA notified
Promedical	COVID-19 Rapid Test (Wondfo SARS-CoV-2 Antibody Test (Lateral Flow Method))						FDA notified
Qingdao Hightop Biotech Co Ltd (China)	SARS-CoV-2 IgM/IgG Antibody Rapid Test	TGA approved 31/03/2020					
RayBiotech, Inc.	Coronavirus (COVID-19) IgM/IgG Rapid Test Kit			CE-marked			
RayBiotech, Inc.	Novel Coronavirus (SARS-CoV-2) IgG Antibody Detection Kit (Colloidal Gold Method)						FDA notified
RayBiotech, Inc.	Novel Coronavirus (SARS-CoV-2) IgM Antibody Detection Kit (Colloidal Gold Method)						FDA notified
Safecare Biotech (Hangzhou) Co., Ltd	SAFECARE COVID-19 IgG/IgM Rapid Test Device						FDA notified
SD Biosensor	STANDARD Q COVID-19 IgM/IgG Duo						FDA notified
Shanghai Eugene Biotech Co., Ltd.	SARS-CoV2 (COVID-19) IgG/IgM Rapid Test						FDA notified
Shenzhen Landwind Medical Co., Ltd	COVID-19 IgG/IgM Rapid Test Device						FDA notified
Shenzhen Watmind Medical Co.	SARS-CoV-2 IgG/IgM Ab Diagnostic Test Kit						FDA notified
Snibe Diagnostic (China)	Maglumi 2019-nCoV (SARS-CoV-2) IgM/IgG kits			CE-marked			
Sugentech, Inc.	SGTi-flex COVID-19 IgM/IgG						FDA notified
Sure Bio-tech API	Covid-Rapid IgM/IgG Antibody Test Kit						FDA notified
Surescreen Diagnostics - antibody manufacturing source is located in China	Covid-19 IgM/IgG Test cassette			CE-marked			
Suzhou Kangheshun Medical Technology Co., Ltd	SARS-CoV-2 IgG/IgM Rapid Test Cassette						FDA notified

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
Telepoint Medical Services	SARS-CoV-2 IgG/IgM Rapid Qualitative Test						FDA notified
Tianjin Beroni Biotechnology Co. Ltd	SARS-CoV-2 IgG/IgM Antibody Detection Kit						FDA notified
United Biomedical, Inc. UBI®	SARS-CoV-2 ELISA						FDA notified
W.H.P.M. Inc.,	COVID-19 IgM/IgG Rapid Test						FDA notified
W.H.P.M. Inc.,	COVISURE™ COVID-19 IgM/IgG Rapid Test						FDA notified
Wuhu 3H Biotechnology Co. Ltd.	COVID-19 IgG/IgM Test Kit (Colloidal Gold Method)						FDA notified
Xiamen AmonMed Biotechnology Co. Ltd	Helix-19 COVID-19 IgM/IgG Test Kit (Colloidal Gold)						FDA notified
Zhejiang GENE SCIENCE Co., Ltd	Novel Coronavirus (2019-nCoV) IgM/IgG Antibodies Detection Kit (Latex Chromatography)						FDA notified
Zhejiang Orient Gene Biotech, Co., Ltd.	COVID-19 IgG/IgM Rapid Test Cassette	TGA approved 01/04/2020					FDA notified
Zhengzhou Fortune Bioscience Co., Ltd.	COVID-19 IgG Antibody Rapid Test Kit (Colloidal Gold Immunochromatography method)						FDA notified
Zhengzhou Fortune Bioscience Co., Ltd.	COVID-19 IgM Antibody Rapid Test Kit (Colloidal Gold Immunochromatography method)						FDA notified
Zhengzhou Fortune Bioscience Co., Ltd.	COVID-19 Antibody Rapid Test Kit (Colloidal Gold Immunochromatography method)						FDA notified
Zhongshan Bio-Tech Co. Ltd	SARS-CoV-2 IgM/IgG (GICA)						FDA notified
Zhuhai Encode Medical Engineering Co., Ltd	Novel Coronavirus (COVID-19) IgG/IgM Rapid Test Device						FDA notified
Zhuhai Livzon Diagnostics, Inc. Diagnostic Kit for IgM/IgG	Diagnostic Kit for IgM/IgG Antibody to Coronavirus (SARS-CoV-2) (Colloidal Gold)						FDA notified
Microfluidic chip							
Shenzhen Shineway Technology, Hong Kong	POCT-PCR			CE-marked			
Microarray tests							

Table A.1 Diagnostic tests currently approved* or authorised for use internationally [Accurate as of 14 April 2020, 13.00 GMT]

Manufacturer	SARS-CoV-2 test	Australia	Canada	Europe*	Singapore	South Korea	US
Veredus Laboratories Pte Ltd	VereCoV™ Detection Kit				Provisional authorisation		
Isothermal							
Biowalker Pte Ltd	Kit for Novel-Coronavirus (2019-nCoV) RNA (Isothermal Amplification-Real Time Fluorescence Assay)				Provisional authorisation		
Antigen test							
Bioeasy (USA)	2019-Novel Coronavirus (2019-nCoV) Antigen Rapid test kit			CE-marked			

NOTE: Data for non-European regions are accurate as of 14 April 2020, 13.00 GMT.

* This list is not exhaustive. Data for Europe are limited to products for which a CE mark is claimed, as detailed in Section 6. Manufacturer/distributor may vary by country.

Appendix B – Manufacturer-reported characteristics of SARS-CoV-2 tests

Table B1. Manufacturer-reported characteristics of NAAT RT-PCR tests for detection of SARS-CoV-2

Manufacturer (country)	Device name	Sample type	Target gene	Test capacity	Runtime	Additional equipment (not provided in test kit)
Anatolia Geneworks (Turkey)	Bosphore Novel Coronavirus (2019-Ncov) Detection Kit	Unclear	E, ORF1ab	Not specified	Not specified	Not specified
BGI Europe (Denmark)	Real-Time Fluorescent RT-PCR kit for detecting 2019-nCoV (SARS-CoV-2)	Throat swab, BALF	Not specified	Not specified	<3 hours	Not specified
CerTest Biotech (Spain)	VIASURE SARS-CoV-2 Real Time PCR Detection Kit	Respiratory swab (nasopharyngeal/ oropharyngeal)	N, ORF1ab	Not specified	Not specified	Thermocycler, RNA extraction kit, Centrifuge for 1.5 mL tubes and PCR-well strips or 96-well, Vortex, Micropipettes (0.5-20 µL, 20-200 µL), Filter tips, Powder-free disposable gloves, Loading block (for use with Qiagen/Corbett Rotor-Gene® instruments)
Co-Diagnostics (US)	Logix Smart COVID-19 Test (RT-PCR)	LRT (BALF, sputum, tracheal aspirate), URT (nasopharyngeal fluids, nasal swab), serum	RdRp	100 rxn	60-90 minutes	Thermocycler, Extraction system, Consumables (e.g. gloves, lab-coat), Micropipettes (5µL to 1000µL), cold block or ice, Vortex and centrifuge, Class II Biosafety cabinet, PCR workstation, Co-Diagnostics Diagnostics Box (Bio Molecular Systems, distributed by Co-Diagnostics, Inc.), Thermocycler with channels capable of detecting FAM and CF610 fluorophores
Credo Diagnostics (Singapore)	VitaPCR COVID-19 assay	Unclear	Not specified	Not specified	20 minutes	Not specified

Manufacturer (country)	Device name	Sample type	Target gene	Test capacity	Runtime	Additional equipment (not provided in test kit)
Genomica (Spain)	qCOVID-19 Real time Multiplex RT-PCR	Unclear	Not specified	48	1 hr 30 minutes	Not specified
Genomica (Spain)	CLART® COVID-19 Real time Multiplex RT-PCR	Unclear	Not specified	80-96	< 5 hours	Not specified
Kogene Biotech (Korea)	PowerChek™ 2019-nCoV Real-time PCR Kit	Unclear	E, RdRp	Not specified	Not specified	Not specified
Liferiver Bio-Tech (China)	Novel Coronavirus (2019-nCoV) Real Time Multiplex RT-PCR kit	URT (nasopharyngeal extracts, deep cough sputum) and LRT (BALF) specimens	E, N, RdRP	Not specified	35-50 minutes	Biological cabinet, Vortex mixer, Cryo-container, Sterile filter tips for micro pipets, Disposable gloves (powderless), Refrigerator and freezer, Real time PCR system, Real time PCR reaction tubes/plates, Pipets (0.5µl – 1000µl), Sterile microtubes, Biohazard waste container, Tube racks, Desktop, microcentrifuge for “eppendorf” type tubes
OSANGHealthcare (Korea)	GeneFinderTM COVID-19 Plus RealAmp Kit	Respiratory samples (BALF, nasopharyngeal/ oropharyngeal swab, sputum)	E, N, RdRp	Not specified	<3 hours	Applied Biosystems® 7500 / 7500 Fast Real Time PCR Instrument System and CFX96 real time PCR system, Pipettes (1- 20 µl, 20-200 µl, 200-1,000 µl), Pipettes tips with aerosol barrier (RNase, DNase-free), Powder-free gloves (disposable), Vortex mixer or equivalent, 1.5 ml tube, PCR tube or 96 well plate, Bench microcentrifuge, RNA isolation kit
Primerdesign Ltd (UK)	Coronavirus (COVID-19) genesig® Real-Time PCR assay	Nasopharyngeal/ oropharyngeal swab, sputum	Not specified	96	Unspecified	PCR hood, Benchtop centrifuge, Vortex mixer, White Roche® LightCycler 480 Multiwell plate 96, White Bio-Rad® CFX96 Multiwell plate 96, Transparent Applied Biosystems® 7500 Real-Time PCR System Multiwell Plate 96, Adjustable pipettes, Pipette tips with filters, Disposable gloves, 1.5ml microcentrifuge tubes for extraction

Manufacturer (country)	Device name	Sample type	Target gene	Test capacity	Runtime	Additional equipment (not provided in test kit)
Roche Molecular Diagnostics (Switzerland)	Cobas® SARS-CoV-2 (Real-Time PCR assay)	Nasopharyngeal/ oropharyngeal swab	E, Orf1a	96	< 3 hours	Unspecified
Sansure (China)	Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit	BALF, nasopharyngeal/ oropharyngeal swab, sputum, whole blood, feces	Orf1a, N	Not specified	30 minutes	1.5 mL Dnase-free and Rnase-free centrifuge tubes, 0.2 mL PCR reaction tubes, pipette tips (10 µL, 200 µL and 1000 µL tips with filters are preferred), desktop centrifuge, desktop vortex mixer various models of pipette gund
SD Biosensor (Korea)	STANDARD M n-CoV Real-Time Detection Kit for emergency COVID-19 test	Nasopharyngeal/throat swabs, sputum	E, ORF1ab, RdRp	Not specified	90 minutes	Unspecified
Seegene (Korea)	Allplex™ 2019-nCoV Assay	BALF, nasopharyngeal/throat swab/aspirate, sputum	E, N, RdRp	Not specified	110 minutes (after extraction)	Unspecified
Solgent	DiaPlexQ™ Novel Coronavirus (2019-nCoV) Detection Kit	Nasopharyngeal/oropharyngeal swab, sputum	N, Orf1a	Not specified	< 2 hours	States all reagents included
Vircell (Spain)	SARS-CoV-2 RealTime PCR kit	Respiratory samples	Not specified	Not specified	90 mins	Unspecified

Note: List is limited to products for which a CE mark is claimed. List is not exhaustive.

Key: BALF – bronchoalveolar lavage fluid; CE – Conformité Européenne; IVD – in vitro diagnostics; LRT – lower respiratory tract; NAAT – nucleic acid amplification test; RT-PCR – reverse transcriptase polymerase chain reaction; URT – upper respiratory tract.

Table B2. Manufacturer-reported sensitivity and specificity of NAAT RT-PCR tests for detection of SARS-CoV-2

Manufacturer (country)	Device name	Analytical sensitivity	Clinical sensitivity (95% CI)	Clinical specificity
Anatolia Geneworks (Turkey)	Bosphore Novel Coronavirus (2019-Ncov) Detection Kit	Not specified	Not reported	Not reported
BGI Europe (Denmark)	Real-Time Fluorescent RT-PCR kit for detecting 2019-nCoV (SARS-CoV-2)	100 copies/mL	Not reported	Not reported
CerTest Biotech (Spain)	VIASURE SARS-CoV-2 Real Time PCR Detection Kit	≥10 RNA copies per reaction	100% (16-100%) Comparator: Molecular detection	100% (96-100%) Comparator: Molecular detection
Co-Diagnostics (US)	Logix Smart COVID-19 Test (RT-PCR)	9.35x1000 copies/ml	100% (96-100%)	100% (96-100%)
Credo Diagnostics (Singapore)	VitaPCR COVID-19 assay	Not specified	Not reported	Not reported
Genomica (Spain)	qCOVID-19 Real time Multiplex RT-PCR	Not specified	100%*	100%*
Genomica (Spain)	CLART® COVID-19 Real time Multiplex RT-PCR	Not specified	96%*	98%*
Kogene Biotech (Korea)	PowerChek™ 2019-nCoV Real-time PCR Kit	Not specified	Not reported	Not reported

Manufacturer (country)	Device name	Analytical sensitivity	Clinical sensitivity (95% CI)	Clinical specificity
Liferiver Bio-Tech (China)	Novel Coronavirus (2019-nCoV) Real Time Multiplex RT-PCR kit	1×1000 copies/ml	Not reported	Not reported
OSANGHealthcare (Korea)	GeneFinderTM COVID-19 Plus RealAmp Kit	10 copies/reaction for all target genes	Not reported	Not reported
Primerdesign Ltd (UK)	Coronavirus (COVID-19) genesig® Real-Time PCR assay	0.58 copies/µl	98% (89-100%) Comparator: Real-time PCR	100% (93-100%) Comparator: Real-time PCR
Roche Molecular Diagnostics (Switzerland)	Cobas® SARS-CoV-2 (Real-Time PCR assay)	Not specified	Not reported	Not reported
Sansure (China)	Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit	200 copies/mL	Not reported	Not reported
SD Biosensor (Korea)	STANDARD M n-CoV Real-Time Detection Kit for emergency COVID-19 test	Not specified	Not reported	Not reported
Seegene (Korea)	Allplex™ 2019-nCoV Assay	100 RNA copies/rxn	URT: 100% (93-100%) LRT: 100% (93-100%) Comparator: Real-time PCR	URT: 94% (87-98%) LRT: 98% (93-100%) Comparator: Real-time PCR

Manufacturer (country)	Device name	Analytical sensitivity	Clinical sensitivity (95% CI)	Clinical specificity
Solgent	DiaPlexQ™ Novel Coronavirus (2019-nCoV) Detection Kit	Not specified	Not reported	Not reported
Vircell (Spain)	SARS-CoV-2 RealTime PCR kit	Not specified	Not reported	Not reported

Key: CI – confidence interval; IVD – in vitro diagnostics; NAAT – nucleic acid amplification test; RT-PCR – reverse transcriptase polymerase chain reaction.
Note: List is limited to products for which a CE mark is claimed and is not exhaustive. All data are as reported by the manufacturer and have not been independently validated. Diagnostic performance has been rounded to the nearest integer.

* Clinical sensitivity and specificity were reported by the manufacturer, but without underlying clinical data. Therefore, 95% confidence intervals could not be estimated.

Table B3. Manufacturer-reported characteristics of antibody tests for detection of SARS-CoV-2 for which a CE mark is claimed

Manufacturer (country)	Device name	Sample type	Target antibody	Sample capacity	Runtime	Additional equipment (not provided in test kit)
Assay Genie (UK)	COVID-19 Rapid POC (Point-of-Care) kit	Whole Blood, serum, plasma	IgG, IgM	1	10-15 minutes	Specimen collection containers, Lancets (for fingerstick whole blood only), Capillary tubes, Centrifuge (for plasma only), Timer, Pipette
Aytu BioScience (China)	COVID-19 IgG/IgM Rapid Test	Whole blood, serum, plasma	IgA, IgG	Not specified	2-10 minutes	Unclear
Bioeasy (USA)	2019-NOVEL CORONAVIRUS (2019-nCoV) IgG/IgM GICA RAPID TEST KIT	Whole blood, serum, plasma	IgG, IgM	1	10-15 minutes	Unclear
Biomedomics (US)	COVID-19 IgM/IgG Rapid Test	Whole blood, serum, plasma	IgG, IgM	1	10-15 minutes	Capillary Samplers, Lancet, Alcohol Wipes, Gloves, Timer
CTK Biotech (US)	OnSite COVID-19 IgG/IgM Rapid Test	Whole blood, serum, plasma	IgG, IgM	Not specified	10 minutes	Unclear
Dynamiker Biotechnology (Tianjin) Co. Ltd (China)	2019 nCOV IgG/IgM Rapid Test	Whole blood, serum, plasma	IgG, IgM	1	10 minutes	Unclear
EUROIMMUN AG (Germany)	ELISA assay for detection of Anti SARS-COV-2	Serum	IgG, IgM	Not specified	Unclear	Unclear

Manufacturer (country)	Device name	Sample type	Target antibody	Sample capacity	Runtime	Additional equipment (not provided in test kit)
InTec Products (US)	Rapid SARS-CoV-2 Antibody Test	Whole blood, serum or plasma (fingerprick)	IgG	1	15-20 minutes	Unclear
InTec Products (US)	Rapid SARS-CoV-2 Antibody (IgM/IgG) Test	Whole blood, serum or plasma (fingerprick)	IgG, IgM	1	15-20 minutes	Unclear
Nal von Minden GmbH (Germany)	Nadal COVID-19 IgG/IgM Test (test cassette)	Whole blood (fingerprick/ venepuncture), serum, plasma	IgG, IgM	1	Unclear	Specimen collection containers (appropriate for specimen material to be tested), Centrifuge (for serum or plasma specimens only), Alcohol pads, Lancets (for fingerstick whole blood specimens only), Timer
Raybiotech (USA)	Coronavirus (COVID-19) IgM/IgG Rapid Test Kit	Whole blood (fingerprick/ venepuncture), serum, plasma	IgG, IgM	Not specified	8-10 minutes (reaction time only)	None
Snibe Diagnostic (China)	Maglumi 2019-nCoV (SARS-CoV-2) IgM/IgG kits	Serum, plasma	IgA, IgM	Not specified	30 minutes	Unclear
Surescreen Diagnostics (UK)	Covid-19 IgM/IgG Test cassette	Whole blood, serum, plasma (fingerprick possible)	IgG, IgM,	1	10-15 minutes	Unclear

Key: IgG – immunoglobulin G; IgM – immunoglobulin M; IVD – in vitro diagnostics.

Note: List is limited to products for which a CE mark is claimed and is not exhaustive. All data are as reported by the manufacturer and have not been independently validated.

Table B4. Manufacturer-reported sensitivity and specificity of antibody tests for detection of SARS-CoV-2 for which a CE mark is claimed

Manufacturer (country)	Device name	Clinical sensitivity (95% CI)	Clinical specificity
Assay Genie (UK)	COVID-19 Rapid POC (Point-of-Care) kit	IgG: 100% (83-100%) IgM: 85% (62-97%)	IgG: 98% (89-100%) IgM: 96% (86-100%)
Aytu BioScience (China)	COVID-19 IgG/IgM Rapid Test	IgG: 97% (85-100%) IgM: 88% (80-94%) Comparator: RT-PCR or clinical diagnosis	IgG: 100% (77-100%) IgM: 100% (77-100%) Comparator: RT-PCR or clinical diagnosis
Bioeasy (USA)	2019-NOVEL CORONAVIRUS (2019-nCoV) IgG/IgM GICA RAPID TEST KIT	Not reported	Not reported
Biomedomics (US)	COVID-19 IgM/IgG Rapid Test	Dual IgG/IgM: 89% (85-92%) Comparator: Single IgG/IgM	Dual IgG/IgM: 91% (84-95%) Comparator: Single IgG/IgM
CTK Biotech (US)	OnSite COVID-19 IgG/IgM Rapid Test	90% (73-98%)**	100% (89-100%)**
Dynamiker Biotechnology (Tianjin) Co. Ltd (China)	2019 nCOV IgG/IgM Rapid Test	90% (73-98%)**	100% (89-100%)**
EUROIMMUN AG (Germany)	ELISA assay for detection of Anti SARS-COV-2	IgA: 93% (78-99%)** IgG: 67% (47-83%)**	IgA: 93% (85-97%)** IgG: 96% (90-99%)**
InTec Products (US)	Rapid SARS-CoV-2 Antibody Test	95%*	98%*
InTec Products	Rapid SARS-CoV-2 Antibody (IgM/IgG) Test	94%*	98%*

Manufacturer (country)	Device name	Clinical sensitivity (95% CI)	Clinical specificity
(US)			
Nal von Minden GmbH (Germany)	Nadal COVID-19 IgG/IgM Test (test cassette)	IgG: 98% (93-100%) IgM: 94% (86-97%) Comparator: RT-PCR or clinical diagnosis	IgG: 99% (96-100%) IgM: 99% (97-100%) Comparator: RT-PCR or clinical diagnosis
Raybiotech (USA)	Coronavirus (COVID-19) IgM/IgG Rapid Test Kit	Not reported	Not reported
Snibe Diagnostic (China)	Maglumi 2019-nCoV (SARS-CoV-2) IgM/IgG kits	Not reported	Not reported
Surescreen Diagnostics (UK)	Covid-19 IgM/IgG Test cassette	IgG: 97% (86-100%) IgM: 89% (72-96%)	IgG: 99% (96-100%) IgM: 99% (95-100%)

Key: CI – confidence interval; IgG – immunoglobulin G; IgM – immunoglobulin M; IVD – in vitro diagnostics.
Note: List is limited to products for which a CE mark is claimed and is not exhaustive. All data are as reported by the manufacturer and have not been independently validated. Diagnostic performance has been rounded to the nearest integer.

* Clinical sensitivity and specificity were reported by the manufacturer, but without underlying clinical data. Therefore, 95% confidence intervals could not be estimated.

** According to data reported by Lassaunière et al.[151] who evaluated nine commercial antibody tests available in Denmark for detection of CoV-SARS-2. The pre-print was not peer-reviewed as of April 15 2020. CTK Biotech reported the clinical sensitivity and specify at 97% and 99%, respectively, but without presentation of underlying clinical data.

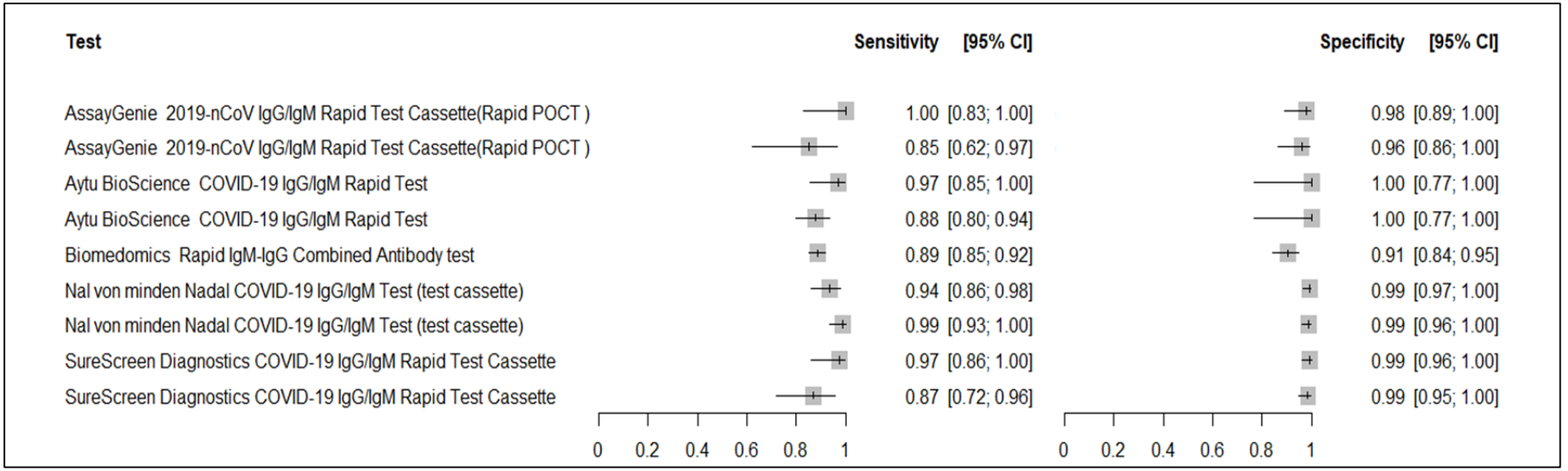
Table B5. Characteristics of other diagnostic tests for detection of SARS-CoV-2 for which a CE mark is claimed

Manufacturer (country)	Device name	Device technology	Target	Sample type	Sample capacity	Turn-around	Additional equipment
Bioeasy (USA)	2019-Novel Coronavirus (2019-nCoV) Antigen Rapid test kit	Fluorescence immuno-chromatographic assay	Viral antigen	Sputum, alveolar lavage fluid, nasal swab	Unspecified	10 mins	Not specified
Shenzhen Shineway Technology (Hong Kong)	POCT-PCR	Microfluidic chip	Viral RNA	Unclear	8 samples	40 mins (sampling to testing)	Not specified

Key: IVD – in vitro diagnostics; PCR – polymerase chain reaction; POCT – point of care test.

Note: List is limited to products for which a CE mark is claimed and is not exhaustive. All data are as reported by the manufacturer and have not been independently validated.

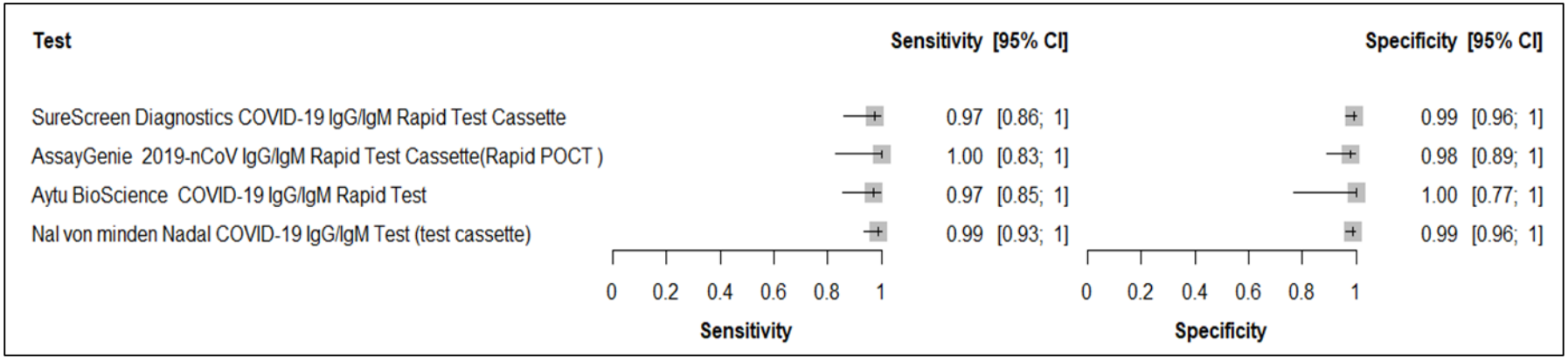
Figure B1. Forest plot of manufacturer-reported antibody tests for detection of SARS-CoV-2* for which a CE mark is claimed



Note: List is limited to products for which a CE mark is claimed and is not exhaustive. All data are as reported by the manufacturer and have not been independently validated. Only estimates where manufacturers reported sufficient data are presented in the forest plot.

* A number of the devices are presented twice because diagnostic accuracy varied according to target antibody (that is, IgG or IgM). Subgroup analysis by antibody target is presented below.

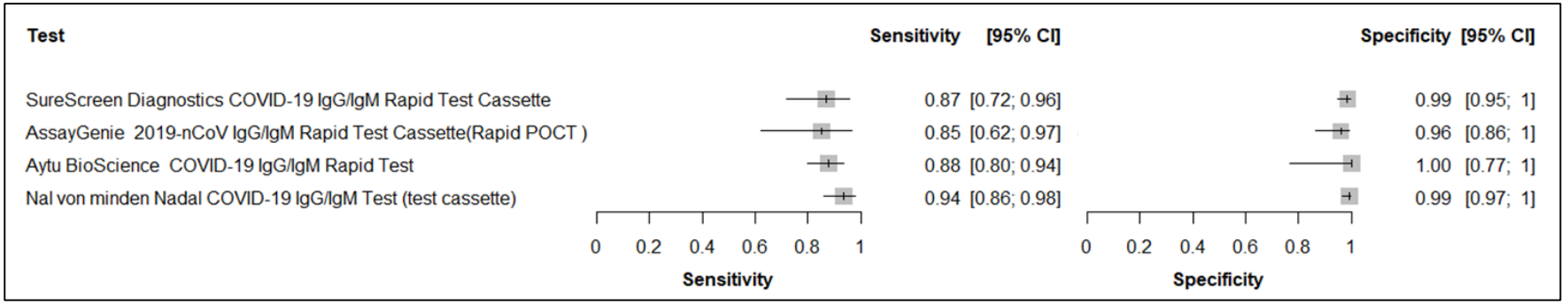
Figure B2. Forest plot of manufacturer-reported antibody tests for detection of SARS-CoV-2 (subgroup analysis of tests for IgG detection)* for which a CE mark is claimed



Key: IgG – immunoglobulin G; IgM – immunoglobulin M.

Note: List is limited to products for which a CE mark is claimed and is not exhaustive. All data are as reported by the manufacturer and have not been independently validated. * Only estimates where manufacturers reported sufficient data are presented in the forest plot.

Figure B3. Forest plot of manufacturer-reported antibody tests for detection of SARS-CoV-2 (subgroup analysis of tests for IgM detection)* for which a CE mark is claimed



Key: IgM – immunoglobulin M.

Note: List is limited to products for which a CE mark is claimed and is not exhaustive. All data are as reported by the manufacturer and have not been independently validated. Only estimates where manufacturers reported sufficient data are presented in the forest plot.

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