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Review

Screening, Diagnostic and Prognostic Tests for COVID-19: A Comprehensive Review

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Abstract: While molecular testing with real-time polymerase chain reaction (RT-PCR) remains the gold-standard test for COVID-19 diagnosis and screening, more rapid or affordable molecular and antigen testing options have been developed. More affordable, point-of-care antigen testing, despite being less sensitive compared to molecular assays, might be preferable for wider screening initiatives. Simple laboratory, imaging and clinical parameters could facilitate prognostication and triage. This comprehensive review summarises current evidence on the diagnostic, screening and prognostic tests for COVID-19.

Keywords: SARS-CoV2; COVID-19; coronavirus; diagnosis; screening; prognosis; PCR; CRISP; immunoglobulin

Citation: Ulinici, M.; Covantev, S.; Wingfield-Digby, J.; Beloukas, A.; Mathioudakis, A.G.; Corlateanu, A. Screening, Diagnostic and Prognostic Tests for COVID-19: A Comprehensive Review. *Life* **2021**, *11*, 561. https://doi.org/10.3390/life11060561

Academic Editor: Patrick Mercié

Received: 21 May 2021
Accepted: 10 June 2021
Published: 14 June 2021

1. Introduction

Declared a pandemic in March 2019, COVID-19, which is caused by the novel severe acute respiratory coronavirus 2 (SARS-CoV-2) has caused not only significant global morbidity (>160 million cases) and mortality (>3.4 million deaths), but also disruption to society and economies [1–4]. The true incidence of COVID-19 is likely to have been underestimated, either due to individuals underreporting mild symptoms or inadequate testing. Screening and diagnostic strategies for COVID-19 have varied worldwide according to government policies, technology, funding, and data management capabilities. Even in industrialised nations, uncertainties in strategy, regulatory hurdles and supply issues have disrupted testing capabilities, possibly contributing to worsening spread of SARS-CoV2. Standardisation and improvement of COVID-19 diagnostics, with more efficient detection and treatment of cases, is likely to be beneficial to both industrialised and low-income nations [5–7]. In this review, we address some of the key concerns regarding laboratory and radiological screening, diagnosis and prognostication that have arisen during the ongoing COVID-19 pandemic [8]. A detailed description of the characteristics of the available screening and diagnostic assays and medical devices is beyond the scope of this manuscript and can be found in the Joint Research Centre of the European Medicines Agency/European Commission (https://covid-19-diagnostics.jrc.ec.europa.eu/devices, accessed on 10 June 2021).

2. Diagnostic Testing

Confirming diagnosis, starting treatment (where necessary) and initiation of social-distancing measures are essential in the management of COVID-19. Numerous methods are utilised for the laboratory diagnosis of viral infections, such as culture, viral nucleic acid detection and serology (i.e., viral antigen or humoral responses) [9]. The most commonly available tests are direct (detection of nucleic acids (i.e., viral genome) or antigens of the virus) and indirect (assessment of serum antibody levels).

2.1. Direct Testing—Molecular Methods

Viral nucleic acid detection, directly detecting genetic material, is the gold standard in diagnostic virology [9]. Two commonly preferred nucleic acid-based detection methodologies are available for the diagnosis of SARS-CoV-2. RT-PCR based methods (real-time polymerase chain reaction (RT-PCR)) are routinely used for diagnosis, while high throughput genome sequencing is used at an unprecedented rate for COVID-19 variants surveillance [10].

RT-PCR has frequently been utilised in the detection of COVID-19 nucleic acids from a number of sources such as posterior oropharyngeal saliva, throat and nasopharyngeal swabs, sputum and bronchial fluid [11]. Moreover, in some cases the virus can be isolated from blood, semen and faeces, even in the absence of a positive respiratory sample [12]. However, a recent systematic review concluded that RT-PCR tests from stool, urine, and plasma were less sensitive than respiratory samples [13].

In spite of RT-PCR being the benchmark for COVID-19 diagnosis, there is a potential for false-negative results, which may be related to the viral load, sampling time or sampling bias. RT-PCR tests typically provide a positive result if the specimen is collected 2–8 days after the onset of the infection [14]. A meta-analysis, which assessed the accuracy of COVID-19 tests and included 34 studies with 12,057 COVID-19 confirmed cases reported false-negative RT-PCR rates between 2% and 29%. The reported sensitivity was 71-98%, based on individuals with an initial negative RT-PCR being subsequently found to have a positive one. COVID-19 diagnostic accuracy may be improved by combining results of RT-PCR, imaging and serology screening [13].

Several other methods, namely, droplet digital PCR (ddPCR) and reverse transcription-loop-mediated isothermal amplification (RT-LAMP), which detect SARS-CoV-2 RNA are being also used to complement RT-PCR. Overall, ddPCR performs better than standard RT-PCR for clinical diagnosis of SARS-CoV-2, reducing false-negative results, although it is less thoroughly evaluated compared to the latter [15,16]. This is further highlighted by evidence showing the ddPCR-based can effectively detect SARS-CoV-2 genome in symptomatic cases with a negative standard RT-PCR [17]. A recently published study reported that combining RT-PCR with ddPCR improves the sensitivity from 40% (95% CI: 27–55%) to 94% (95% CI: 83–99%) without limiting the specificity, which remains 100% (95% CI: 48–100%), leading to an overall increase in the diagnostic accuracy from 47% (95% CI: 33–60%) to 95% (95% CI: 84–99%) [16].

Rapid diagnosis of COVID-19 is important, and some methods provide a result in less than an hour. RT-LAMP detects SARS-CoV-2 RNA in approximately 30 min with good correlation to the conventional RT-PCR, allowing for rapid delivery of results to patients both in the hospital and community settings [18]. RT-LAMP has been reported to have high sensitivity and specificity, operational simplicity and low cost [19].

Data on analytical performance (i.e., sensitivity, specificity, lower limits of detection (LOD), etc.) for all commercially available molecular assays are provided by FIND (a global alliance for diagnostics, which seeks to ensure equitable access to reliable diagnosis around the world) and can be assessed in the following directory, which is regularly updated (https://www.finddx.org/test-directory/, accessed on 10 June 2021).

Alternative approaches based on combinations of isothermal amplification and clustered regularly interspaced short palindromic repeats (CRISPR) such as the SHERLOCK (specific high-sensitivity enzymatic reporter unlocking) technique reduce dependence on