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Cell & Cellular Life Sciences Journal
ISSN: 2578-4811

Current Diagnostics of SARS-CoV-2

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Mini Review

Volume 5 Issue 2

Received Date: October 01, 2020

Published Date: October 13, 2020

DOI: 10.23880/cclsj-16000157

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Abstract

The COVID-19 pandemic has caused an unprecedented global health and economy crisis and it can potentially become a seasonal disease. Vaccines are still considered the most crucial solution, but it takes a long time to develop an effective vaccine. Therefore, the COVID-19 testing has become a strong weapon to identify infections and help control the virus spread and fight against the pandemic. Currently, there are a variety of testing formats for different purposes approved by the FDA. Here, we outline some key questions regarding current COVID-19 testing.

Keywords: COVID-19; World Health Organization; Rapid Point-of-Care

Abbreviations: SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; NAAT: Nucleic Acid Amplification Tests; ORF: Open Reading Frame; RDRP: RNA-Dependent RNA Polymerase; RT-LAMP: Reverse Transcription Loop-Mediated Isothermal Amplification; EUA: Emergency Use Authorization; POC: Rapid Point-of-Care.

Introduction

In December 2019, a pneumonia outbreak with an unknown cause was reported from a seafood wholesale market in Wuhan, China [1]. It turned out that the outbreak was caused by a novel coronavirus, which was subsequently named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), and the disease associated with the viral infection referred to as "Coronavirus Disease 2019" (COVID-19). This deadly virus soon spread rapidly throughout China and thereafter the whole world, escalating into an unprecedented pandemic. On January 30, 2020, the World Health Organization (WHO) declared a global health emergency. To date, there have been over 30 million confirmed cases reported, including 948,000 deaths [2]. Rapid and accurate testing has played an increasingly important role in helping to contain viral pandemics. They not only help identify those infected but also contribute to treatment decisions and support efforts aimed at controlling the spread of the disease. In this article, we will discuss some key questions regarding currently available tests for SARS-CoV-2.

What is the Purpose of Current Testing?

There are three main reasons for testing for SARS-CoV-2 infection:

- Diagnosis of COVID-19 disease,
- Screening of asymptomatic individuals, and
- Surveillance for guiding public health interventions.

Diagnostic tests are used to identify the presence or absence of SARS-CoV-2 at an individual level when a person displays symptoms or is suspected of being infected from exposure to COVID-19 patients. The purpose of screening tests is to detect the occurrence of the disease in large numbers of asymptomatic individuals, which can help identify early signs of health problems, reduce spread, and clear individuals for return to work or school. Surveillance testing is generally used to monitor for community or population-level outbreaks, or to determine the incidence or prevalence of viral infection in the community. Thus, surveillance testing is used to gain information at a population level rather than an individual level. Results from surveillance testing are often returned in aggregate to a requesting institution. The key differences are listed in Table 1 [3].

	Diagnostic	Screening	Surveillance
Symptomatic or Known or Suspected Exposure	Yes	No	N/A
Asymptomatic without Known or Suspected Exposure	No	Yes	N/A
Characterize Incidence and Prevalence in the Community	N/A	N/A	Yes
Results may be Returned to Individuals	Yes	Yes	No
Results Returned in Aggregate to Requesting Institution	No	No	Yes
Results Reported to State Public Health Department	Yes	Yes	Only if requested; must be in aggregate
Testing can be performed in a CLIA-Certified Laboratory	Yes	Yes	Yes
Testing can be performed in a Non-CLIA-Certified Laboratory	No	No	Yes
Test System Must be FDA Authorized or Offered under the Policies in FDA's Guidance	Yes	Yes	No

Table1: Testing Strategies for SARS-CoV-2.

What Types of Samples are used in Testing?

Positive rates vary by sample type, as shown by a study examining 1070 specimens collected from 205 patients with COVID-19. Bronchoalveolar lavage fluid specimens showed the highest positive rates (14/15; 93%), followed by sputum (75/104; 72%), nasal swabs (5/8; 63%), fibrobronchoscope brush biopsy (6/13; 46%), pharyngeal swabs (126/398; 32%), feces (44/153; 29%), blood (3/307; 1%), and urine (0/72; 0%) [4].

Although nasopharyngeal swabs still represent the current gold standard sample type for SARS-CoV-2 testing, saliva tests have recently drawn attention since they offer an option for non-invasive sample collection, thus alleviating patient discomfort and lowering the risk posed to healthcare workers [5]. A meta-analysis of saliva testing studies reported 91% (95%CI = 80%-99%) sensitivity for saliva tests and 98% (95%CI 89%-100%) sensitivity for nasopharyngeal swab tests in previously confirmed COVID-19 infected patients, with moderate heterogeneity among studies [6]. Another study showed that saliva samples yielded greater detection sensitivity and less variability than nasopharyngeal swab samples [7]. Because saliva collection can be done without healthcare professionals, saliva-based tests open the door to wider scope of testing including self-testing at home.

Since screening samples from a large population requires a high demand for reagent kits, some studies use a pooled testing method. Published results show that individual positive samples can be detected in pools of up to 32 or even possibly 64 samples with sufficient detection sensitivity, providing great potential in increasing testing capacity for population-wide screening [8].

What Targets Do the Tests Detect?

Three different types of tests are currently available based on different target types: nucleic acid amplification tests (NAAT), antigen tests, and antibody tests. The current gold standard for COVID-19 diagnostic testing is real-time reverse transcription PCR (RT-PCR), which is a NAAT-based test that directly detects the target genes of the SARS-CoV-2. Different assays amplify different regions of the SARS-CoV-2 genome, including the nucleocapsid (N), envelope (E), and spike (S) genes, and/or regions in the first open reading frame (Orf), including the RNA-dependent RNA polymerase (RdRp) gene [9]. RT-PCR is highly sensitive and robust; however, the turn-around time can take one day or more depending on the number of samples and processing capability of a central

lab. In addition, reagents are prone to shortages due to the overwhelming need for tests [10].

Reverse transcription loop-mediated isothermal amplification (RT-LAMP) represents an alternative to RT-qPCR. RT-LAMP uses different reagents, occurs at a constant temperature (60-65°C) and is completed within 30 minutes. There are many successful examples of this type of test, such as DETECTR [11] and SHERLOCK [12]. Another type of NAAT involves next-generation sequencing for high-throughput diagnostics of SARS-CoV-2, such as Illumina COVID Seq, which has received Emergency Use Authorization (EUA) from the FDA [13].

Antigen tests detect proteins from the SARS-CoV-2 virus from a nasal or throat swab sample to determine if the person has an active infection. Antigen tests are usually very rapid and can report results in minutes [14]. However, antigen tests are usually less sensitive than NAAT-based tests, meaning that they have a higher risk of producing false-negative results [14]. A PCR test may be needed to confirm a negative antigen test result.

Antibody tests or serological tests look for the antibody molecules in blood samples that the human body produces after a person has been infected by the SARS-CoV-2 virus. Antibodies usually take days to develop and may be detectable generally 5-14 days after symptom onset, although immunocompromised individuals may have a delayed antibody response [15]. Studies have shown that asymptomatic individuals demonstrate a weaker immune response to SARS-CoV-2 infection [16] than symptomatic individuals, and also that antibodies decay rapidly in those with mild COVID-19 symptoms [17]. Therefore, such tests are likely of limited efficacy in the early stage of infection.

Where are Tests Performed?

Currently, most COVID-19 tests are performed in a central laboratory environment. Samples are collected by healthcare workers at the sample collection site and then transported to a central laboratory for testing. Results must be reported for all diagnostic and screening testing within 24 hours of test completion [18]. The entire process from sample-to-result usually takes several days, which can significantly delay the diagnosis of COVID-19.

Rapid point-of-care (POC) tests can help meet the urgent need for widespread testing. POC tests are performed in resource-limited settings outside of the laboratory, such as in homes, at work, or in schools, as well as in outpatient clinical settings such as the emergency department or doctor's office. This type of test can increase detection capacity and therefore help control the spread of the virus. Some examples of POC tests that have received EUA from the FDA include Abbott ID Now COVID-19 [19], Abbott BinaxNOW COVID-19 Ag Card [20], Cepheid's Xpert Xpress SARS-CoV-2 [21], Accula SARS-Cov-2 Test [22], Cue COVID-19 Test [23], Sofia 2 SARS Antigen FIA [24]. Currently, there are no FDA-authorized COVID-19 serology point-of-care tests [25].

There is still no cure for COVID-19, and we may also have to wait for some time before an effective vaccine is developed. Hence, we cannot overemphasize the importance of testing in the fight against COVID-19. It is especially critical to identify people who are asymptomatic but may still be spreading the virus. To date, there have been more than 100 million tests reported in the USA, with an overall 8% positive ratio [26]. Testing at a massive scale and repeatedly over time creates an urgent need for the development of rapid and low-cost tests. Large-scale testing combined with measures such as facial coverings (masks) and social distancing will be required before we can safely reopen society and allow the global economy to recover.

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