Testing For SARS-CoV-2: The Day the World Turned its Attention to the Clinical Laboratory

Xuemei Zhao, Julia F. Markensohn, David A. Wollensak and Omar F. Laterza

In the last few months, an unprecedented number of laboratory tests for coronavirus disease 2019 (COVID-19) have been developed at a remarkable speed. With the rapid adoption of these tests into clinical practice, combined with the widespread publicity they received, questions arose related to the different types of tests, their utility, performance, and regulatory approval status. The aim of this publication is to provide a general landscape of laboratory testing for COVID-19 and offer a historical and regulatory perspective associated with them. Specifically, we aim to elaborate on the regulatory complexities of diagnostic testing in the United States and its implications to the present outbreak, as well as provide a synopsis of laboratory tests that have been developed for COVID-19. We will first address the detection of severe acute respiratory syndrome-coronavirus 2 directly by either nucleic acid amplification tests or by the detection of the viral protein for active infections. Subsequently, we will provide an overview of serological tests that can aid not only in diagnosis but additionally help to identify prior infections and potential immunity.

With the emergence in late 2019 of the disease that was eventually named coronavirus disease 2019 (COVID-19), now known to be caused by the novel coronavirus severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), scientists quickly mobilized to develop tests that could aid in the diagnosis of the disease. The virus rapidly spread across the world and, as it did, diagnostic testing took a center stage not only for the scientific community, but for the world at large. By the time the disease was classified as a pandemic, the world, perhaps like in no other time in history, focused its attention and hope to diagnostic testing. Under such scrutiny, it became apparent, particularly in the United States, that testing needs were outpacing the availability of diagnostic tests. To meet the urgency of the situation, regulatory agencies and testing laboratories/manufacturers took on processes that cut the typical diagnostic development timeline. As the process was streamlined, an expansion of testing capabilities occurred. However, the fast pace at which these products made their way into patient care and disease surveillance necessitates a thorough understanding and review of the various platforms. The development of tests related to COVID-19 is evolving rapidly, with new tests becoming available weekly. In this review, we aim to cover tests developed up to May 15, 2020.

CLINICAL LABORATORY REGULATORY CONSIDERATIONS

Under normal circumstances in the United States, a clinical laboratory (medium to high complexity) can deploy a laboratory developed test when the test has received approval under the Clinical Laboratory Improvements Amendment (CLIA) provisions, overseen by Centers for Medicaid and Medicare Services (CMS). In this scenario, the laboratory must demonstrate analytical validity of the test, but not clinical validity. A company that is looking to develop a clinical diagnostic device (in vitro diagnostic (IVD)) for widespread testing would have to seek approval from the US Food and Drug Administration (FDA) under its regulated medical device oversight. The FDA approval for novel IVDs can be a lengthy process, taking approximately a year for a Premarket Approval. However, when a public health emergency was declared by the Secretary of Health and Human Services on February 4, 2020, it gave the FDA the authority to issue an emergency use authorization (EUA) of IVDs for detection and/or diagnosis of the virus that causes COVID-19. Considering the rapid spread of the disease and insufficient testing capacity, the FDA issued several revisions to the EUA policy in order to expedite the development of tests. The first updated policy was published on February 29, 2020. The revised policy enabled test developers seeking EUA approval to begin running their test (in medium to high complexity laboratories) prior to approval. However, the test must be submitted to the FDA for EUA within 15 days of the start of testing.1 With numbers continuing to climb, the FDA further amended the EUA policy on March 16, 2020. The new guidance set forth policies that allowed states more autonomy and test oversight, as well as further details around EUA process of serology tests.2 All of these changes were a significant step in expanding the US testing capacity; however, other challenges to supply chains have prevented the widespread adoption of testing that would...
enable greater viral surveillance. The FDA continues to revise this policy and provide immediate online updates. The latest revision prior to this publication was posted online on May 11, 2020. It includes recommendations on the use of positive clinical samples for clinical validation and it incorporates the use of templates to facilitate the preparation, submission, and authorization of an EUA.

NUCLEIC ACID AMPLIFICATION TESTS

Nucleic acid amplification tests (NAATs) can be a highly sensitive and specific method to detect viral genomic material in various biological specimens. Real-time, reverse-transcriptase polymerase chain reaction (RT-PCR) assays are a deployable and common NAATs and have been developed to detect SARS-CoV-2 RNA in upper and lower respiratory specimens from suspected cases. The specificity of the assay is mostly dependent on primer and probe sequence, whereby the polymerase chain reaction (PCR) primers and probe should have exceedingly better homology to the target sequence than other genomic material present in the sample. Ideally, the target sequence should also have homology to all known circulating strains of the virus. During the course of transmission, it is possible that there is a shift in the target viral sequence, whereby the sensitivity of the assay is compromised due to the

| Date               | Event            | Country | Institution/ company | Target genes | Comments                                                                 |
|--------------------|------------------|---------|----------------------|--------------|--------------------------------------------------------------------------|
| January 24, 2020   | Publication      | China   | Jin Yin-tan Hospital | ORF1ab/RdRp  | Published paper on the initial outbreak in Wuhan\(^5\)                   |
| January 24, 2020   | CFDA approved    | China   | China CDC            | S E N        | Either ORF1ab or N gene must be detected for a clinical positive result\(^19\) |
| January 26, 2020   | NMPA approved    | China   | BGI                  | S E          | One of the first tests approved in China\(^20\)                          |
| February 18, 2020  | KFDA approved    | South Korea | Seegene            | S E N        | Nucleic acid amplification tests (NAATs)                                |
| January 17, 2020   | Publication      | Germany | Charité University   | S E          |                | Nucleic acid amplification tests (NAATs)                                |
| January 31, 2020   | Launch           | Switzerland | Roche             | S E          |                | Nucleic acid amplification tests (NAATs)                                |
| February 17, 2020  | CE-marked        | UK      | Primerdesign        | S E          |                | Nucleic acid amplification tests (NAATs)                                |
| February 4, 2020   | FDA EUA issued   | US      | CDC                  | S E          | CDC test originally included N1, N2, and N3 primers, but dropped N3 on 03/15/2020 |
| February 29, 2020  | FDA EUA issued   | US      | Wadsworth Center New York State DOH | S E          | Targets N1 and N2 regions within N gene                                |
| March 13, 2020     | FDA EUA issued   | US      | Thermo Fisher       | S E          | Targets 3 regions of the N gene                                       |
| March 16, 2020     | FDA EUA issued   | US      | Labcorp             | S E          | Targets N1 and N3 regions                                              |
| March 17, 2020     | FDA EUA issued   | US      | Quest               | S E          | ID NOW COVID-19 diagnostic                                             |
| March 27, 2020     | FDA EUA issued   | US      | Abbott              | S E          | Capable of detecting SARS-CoV-2 with saliva with same assay as Thermo Fisher |
| May 7, 2020        | FDA EUA issued   | US      | Rutgers University  | S E          | Capable of detecting SARS-CoV-2 with saliva with same assay as Thermo Fisher |

CDC, Centers for Disease Control and Prevention; CFDA, China Food and Drug Administration; DOH, Department of Health; E, SARS-CoV-2 envelope structural protein; EUA, emergency use authorization; EUL, Emergency Use Listing; FDA, US Food and Drug Administration; N, SARS-CoV-2 nucleocapsid structural protein; NAAT, nucleic acid amplification test; NMPA, National Medical Product Agency; RdRp, SARS-CoV-2 RNA-dependent RNA polymerase; S, SARS-CoV-2 spike structural protein; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2; WHO, World Health Organization.

*Diagnostic information and approval dates for United States tests are drawn from the FDA database for EUA listings.*
alteration in viral genomic sequence. In order to fully assess all of these considerations when developing an NAAT, the complete genomic sequence of the virus must be known. By early January 2020, the complete sequence of a novel human coronavirus (SARS-CoV-2) was submitted to the National Center for Biotechnology Information (NCBI) GenBank online repository, enabling researchers around the world to begin designing NAAT assays.\(^5\)

The first RT-PCR assay deployed in the United States was developed by the Centers for Disease Control and Prevention (CDC; Table 1). The assay was originally designed to amplify three regions within the nucleocapsid gene of SARS-CoV-2. The test was approved by the FDA for EUA on February 4, 2020, and authorized to be run in laboratories designated by the CDC and CLIA-certified (United States only) to perform high complexity tests. Shortly thereafter, laboratories running the test had begun to observe an issue; the negative control reactions were yielding a positive signal. The issue was not resolved until several weeks later. On March 15, 2020, the FDA amended the EUA authorization of the CDC 2019-nCoV Diagnostic Panel to remove the N3 primer probe set (identified as the root cause of the technical issue) and provided additional information on assay reagents and quality control. In the time between the distribution of the original CDC test and the amendment, only two companies and one state healthcare system gained EUA approval for testing.\(^5\) Since March 15, 2020, over 30 unique NAATs for the detection of SARS-CoV-2 have been developed, which detect different regions of the viral genome (Table 1). Along with the recent EUA approvals, the World Health Organization (WHO) also identified two tests for their Emergency Use Listing procedure: the genesig Real-Time PCR Coronavirus (COVID-19) (PrimerDesign) and cobas SARS-CoV-2 Qualitative assay (Roche).\(^7\) The Emergency Use Listing initiative compiles the different products in the market and assesses their quality and performance; thus, offering different countries and institutions an opportunity to more easily navigate through products that become rapidly marketed.

In addition to RT-PCR, Abbott has recently introduced a molecular point-of-care NAAT that uses isothermal amplification to identify the presence of SARS-CoV-2 in nasal, nasopharyngeal, and throat swabs (iDNow, COVID-19).\(^8\) Isothermal amplification is capable of amplifying RNA targets at a single temperature, thus eliminating the need for more elaborate PCR machines, which require multiple rounds of cycling at different temperatures. Due to this, results can be reported in less than 15 minutes.

The analytical validation used contrived samples of purified viral RNA spiked in to presumed negative nasopharyngeal swab matrix. The limit of detection was established at 125 genome equivalents/mL. Inclusivity and cross-reactivity were determined using only in silico analyses and found to have 100% specificity to all known strains of COVID-19, and no predicted cross-reactivity with other common human pathogens or other coronaviruses. Subsequent to the development and EUA approval of the iDNow test, in May 2020, the FDA provided updated submission templates for laboratories seeking EUA approval. Specifically, it is now recommended that a clinical evaluation be performed on 30 negative and 30 positive COVID-19 specimens, with the positive comparator assay being an already EUA approved RT-PCR test. As more clinical specimens and tests become available, laboratories can anticipate a more rigorous expectation of assay validation for EUA approval.

**VIRAL ANTIGEN TESTS**

Traditionally, both molecular tests and antigen tests can be used to diagnose active viral infections and the same applies for COVID-19. The FDA defines SARS-CoV-2 antigen tests as those that detect proteins that are part of the SARS-CoV-2 virus directly from clinical specimens.\(^4\) The FDA recommends that the following validation studies be conducted for a SARS-CoV-2 antigen test: limit of detection/analytical sensitivity, cross-reactivity/analytical specificity, microbial interference, and clinical agreement study. Antigen tests detect the earliest traces of the virus rather than the genetic code of the virus itself. NAAT-based molecular diagnostic tests had the advantage that assays could be developed as soon as the viral RNA sequence was published in early January 2020. The direct detection of viral protein using immunoassays, however, requires the generation of high-quality antibodies against relevant antigen protein, which takes a few months in addition to assay development and validation time.

As of May 15, 2020, there was only one severe acute respiratory syndrome antigen test (Sofia 2 SARS Antigen FIA) gained EUA by the FDA.\(^3\) It is an immunochromatographic-based lateral flow rapid test with reader developed by Quidel Corporation (San Diego, CA) and was authorized on May 8, 2020. The nucleocapsid protein antigen from SARS-CoV-2 in nasopharyngeal and nasal swab specimens can be qualitatively detected directly or after the swabs have been added to viral transport media in 15 minute test turnaround time (TAT) with reported 80% sensitivity and 100% specificity. This test does not differentiate between SARS-CoV and SARS-CoV-2. Globally, a limited number of SARS-CoV-2 viral antigen tests have been developed, such as the lateral flow-based antigen test developed by SD Biosensor in the Republic of Korea, which is CE marked with comparable sensitivity and specificity to the Quidel test. Compared to NAATs for current viral infection, the immunoassay-based antigen tests are cheaper, easier to use, and, in general, have a shorter TAT. This could potentially ramp up testing capacity by scaling to test millions of individuals daily.

**SEROLOGICAL TESTS**

In contrast to the molecular diagnostic tests and antigen diagnostic tests, which can detect current viral infections, blood-based serological diagnostic tests can inform on prior infections. The FDA defines SARS-CoV-2 serological tests as tests that identify antibodies (e.g., IgG and IgM) to SARS-CoV-2 from clinical specimens.\(^4\) The FDA recommends that the following validation studies be conducted for a SARS-CoV-2 serological assay: cross-reactivity/analytical specificity, class specificity, and clinical agreement study. Unlike NAATs, which solely rely on viral RNA sequence for their development, the development of an immunoassay-based serological tests require certain
| Date     | FDA EUA issued | Developer                     | Device                                                                 | Analyte (antibody to SARS-CoV-2) | Platform              | Capture reagent (SARS-CoV-2 protein antigen) | Reported sensitivity | Reported specificity |
|----------|----------------|-------------------------------|------------------------------------------------------------------------|----------------------------------|-----------------------|---------------------------------------------|----------------------|----------------------|
| April 1, 2020 | Cellex, Inc. (Research Triangle Park, NC) | qSARS-CoV-2 IgG/IgM Rapid Test | IgM and IgG (duplex)                                                   | Lateral flow                   | Not disclosed                      | Nucleocapsid                                  | 93.8%                | 96.0%                |
| April 14, 2020 | Chembio Diagnostic Systems, Inc. (Medford, NY) | DPP COVID-19 IgM/IgG System | IgM and IgG (duplex)                                                   | Lateral flow with reader        | Nucleocapsid                                  | 93.5% 94.4%              |                      |                      |
| April 14, 2020 | Ortho-Clinical Diagnostics, Inc. (Rochester, NY) | qSARS-CoV-2 TOTAL REAGENT PACK AND CALIBRATOR | Pan-Ig                                                                  | High throughput ELISA           | Spike protein S1 subunit             | 100.0% 100.0%              |                      |                      |
| April 15, 2020 | Mount Sinai Hospital Clinical Laboratory (New York, NY) | Mt. Sinai Laboratory COVID-19 ELISA Antibody Test | IgG                                                                    | 2-step ELISA                   | Spike protein (receptor binding domain in screening ELISA, full-length in confirmatory ELISA) | 92.5% 100.0%              |                      |                      |
| April 24, 2020 | AutoBio Diagnostics Co., Ltd. (China; distributed by Hardy Diagnostics in Santa Maria, CA) | Anti-SARS-CoV-2 Rapid Test | IgM and IgG (duplex)                                                   | Lateral flow                   | Not disclosed                      | 99.0% 99.0%               |                      |                      |
| April 24, 2020 | Ortho-Clinical Diagnostics, Inc. (Rochester, NY) | qSARS-CoV-2 TOTAL REAGENT PACK AND CALIBRATOR | IgG                                                                    | High throughput ELISA           | Spike                                | 87.5% 100.0%              |                      |                      |
| April 24, 2020 | DiaSorin Inc. (Italy/USA, Stillwater, MN) | LIAISON SARS-CoV-2 A1/S2 IgG | IgG                                                                    | High throughput ELISA           | Spike protein S1 and S2 subunits     | 97.6% 99.3%               |                      |                      |
| April 26, 2020 | Abbott Laboratories Inc. (Abbott Park, IL) | SARS-CoV-2 IgG assay | IgG                                                                    | High throughput ELISA           | Nucleocapsid                         | 100.0% 99.6%              |                      |                      |
| April 29, 2020 | Bio-Rad Laboratories (Redmond, WA) | Platelia SARS-CoV-2 Total Ab assay | Pan-Ig                                                                  | ELISA                           | Nucleocapsid                         | 92.2% 99.6%               |                      |                      |
| April 30, 2020 | Wadsworth Center, New York State Department of Health (Albany, NY) | New York SARS-CoV Microsphere Immunossy for Antibody Detection | Pan-Ig                                                                  | ELISA                           | Full-length nucleocapsid (N) protein from SARS-CoV-1 antigen (90% sequence homology with SARS-CoV-2 N protein) | 88.0% 98.8%              |                      |                      |
| May 2, 2020 | Roche Diagnostics (Indianapolis, IN) | Elecsys Anti-SARS-CoV-2 | Pan-Ig                                                                  | High throughput ELISA           | Nucleocapsid                         | 100.0% 99.8%              |                      |                      |
| May 4, 2020 | Euroimmun US Inc. (Mountain Lakes, NJ) | Anti-SARS-CoV-2 ELISA (IgG) | IgG                                                                    | ELISA                           | Spike protein S1 subunit             | 90.0% 100.0%              |                      |                      |

COVID-19, coronavirus disease 2019; ELISA, enzyme-linked immunosorbent assay; EUA, emergency use authorization; FDA, US Food and Drug Administration; SARS-CoV-2, severe acute respiratory syndrome–coronavirus 2.

*Reported sensitivity and specificity for IgG and IgM duplex tests are for the combined IgG and IgM antibodies to SARS-CoV-2.
understanding of the human immune response against the different viral proteins in order to select the right capture antigen. In general, viral coat protein is selected owing to its ability to induce response from the immune system. The SARS-CoV-2 spike and nucleocapsid proteins are popular candidates as capture antigens. The spike protein is expressed on the viral surface and mediates cellular entry through the ACE2 cell surface receptor, and, therefore, likely to elicit the highest neutralizing antibody response. The nucleocapsid protein is the most abundant protein in coronaviruses, involved in forming and maintaining highly ordered viral RNA conformation suitable for replicating and transcribing the viral genome, and is highly immunogenic.

As of May 15, 2020, there were 12 qualitative SARS-CoV-2 serological tests that gained EUA by the FDA limited to CLIA-accredited laboratories (Table 2). Some of these tests also received CE mark and/or were approved in other countries such as the United Kingdom. Globally, many SARS-CoV-2 serological tests were CE marked and/or approved in other countries, such as China, Republic of Korea, Singapore, India, Brazil, and Australia. In addition, hundreds of nonapproved tests were developed for research and surveillance use only with limited data disclosed on analytical and clinical validation.

Table 2 illustrates that among the 12 tests that received FDA EUA, 3 are lateral flow rapid tests, 5 are high throughput enzyme-linked immunosorbent assay (ELISA) tests on analyzers, and 4 are traditional ELISA tests. The three lateral flow tests are IgG/IgM duplex tests, whereas the nine ELISA tests are single-plex tests detecting either total antibodies or IgG only to SARS-CoV-2. In general, serum and plasma are the intended specimens in these tests except two ELISA tests that were only authorized in serum under EUA. In addition, fingerprick and/or venipuncture whole blood are also the intended specimens in the three lateral flow tests. The test TAT is 15–20 minutes for lateral flow rapid tests, 2–4 hours in general for traditional ELISA tests, and varies in between for high throughput ELISA tests on analyzers. Interestingly, among 10 tests whose capture antigen information were disclosed, half of them used the spike protein as capture antigen, whereas the other half used the nucleocapsid protein. Furthermore, the selection of either the spike or nucleocapsid protein did not appear to influence test clinical performance. In general, the EUA authorized diagnostic tests have desirable performance characteristics with reported sensitivity and specificity ranging from 87–100% and 94–100%, respectively. In contrast, clinical performance for unauthorized serological tests has a different landscape. Due to urgency and critical public health need, the revised policy issued by the FDA on March 16, 2020, allowed commercial manufacturer to develop and distribute tests prior to EUA submission. After false claims and accuracy problems among the 160 SARS-CoV-2 serological tests launched in the United States, the FDA tightened rules on May 4, 2020, and eventually issued the latest, revised policy for COVID-19 tests on May 11, 2020.

Sero logical tests are being discussed daily in the media globally as they could play an essential role in assessing the prevalence of COVID-19 and frequency of asymptomatic infection, determining who may donate blood as a possible convalescent plasma therapy, and could offer an insight into potential immunity, which could help public policy makers lift the social distancing restrictions. At this moment, however, it is unknown what percentage of the infected population develops an adaptive immune response to SARS-CoV-2, whether they are neutralizing or protective, and for how long antibodies may persist in the body after infection. Furthermore, it is still not entirely clear whether an adaptive immune response translates into durable immunity. In this regard, the WHO issued a warning on April 17, 2020, stating there is no evidence that serological tests can show whether a person has immunity or is no longer at risk of becoming re-infected.

Regardless of this uncertainty, there has been an emphasis on elucidating antibody response against SARS-CoV-2. On March 29, 2020, the American Enterprise Institute issued a report “National coronavirus response: A road map to reopening.” The first point in this report emphasized better data to identify areas of spread and the rate of exposure and immunity in the population in order to gradually move away from a reliance on physical distancing as our primary tool for controlling future spread. Globally, discussions on the concept of immunity certificate (e.g., immune passport) was initiated shortly after the staying at home order was issued in multiple countries. Italy and Germany are pioneering surveillance studies to understand population immunity. In the United States, the first large-scale community based antibody testing study was conducted for 3,439 individuals in Santa Clara County, CA, in early April. Data from a lateral flow based serological test (Premier Biotech, Minneapolis, MN) suggested 2.8% seroprevalence of antibodies to SARS-CoV-2. In New York, on May 2, 2020, Governor Andrew Cuomo announced the results of the largest survey in the nation. The completed antibody testing study showed 12.3% of 15,000 tested individuals has COVID-19 antibodies. As expected, prevalence is highly region-specific across the state with 19.9% positive in New York City. Despite high prevalence of COVID-19 antibodies in New York City, questions remain around immunity. On May 15, 2020, Boston officials released that, among 750 asymptomatic individuals in some of the neighborhoods hardest hit by the ongoing pandemic, 9.9% tested positive for antibodies and 2.6% tested positive for the virus. Furthermore, to expand the scope and time frame of an ongoing COVID-19 antibody study of 36,000 samples funded by the National Institutes of Health, on May 18, 2020, the CDC announced the plan to launch a nationwide study in June or July of up to 325,000 individuals in 25 metropolitan areas to track how COVID-19 antibodies evolve over 18 months across the country.

It is clear that COVID-19 immunity needs to be better understood before it can be used in shaping policy on social distancing. Furthermore, a better understanding of the possibility of immune antibody-dependent enhancement and virus reactivation is also needed, such as those reported in South Korea. The clinical utility of antibodies to SARS-CoV-2 will be a subject of intense investigation in the near future and an area in which well-characterized and highly performing serological assays can help a great deal.
CONCLUSION

It has been difficult to observe the spread of this disease and the devastation it brought to many aspects of society. It has also been remarkable to observe the scientific community mobilized research efforts; from quickly identifying the pathogen and sequencing its genome, to developing diagnostics tools, to offering insights into the development of potential therapeutic interventions and vaccines.

Despite shortcomings in the availability of diagnostics tools and initial quality of first-generation assays, the field remains committed to overcoming these early challenges and implementing readily available, high quality diagnostics. Diagnostics will continue to play a critical role in every aspect of the disease: from diagnosing new and prior infections, to enhanced understanding of disease spread, to containment of disease transmission, to insights into immunity and the enablement of therapeutic and vaccine development that will finally bring the pandemic under control.

The research and development of novel or improved diagnostic tests for COVID-19 will undoubtedly continue to move at an incredibly fast pace. We recommend visiting the FDA and CDC websites for the latest updates.

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