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COVID-19 laboratory testing issues and capacities as we transition to surveillance testing and contact tracing

As of May 19, 2020, 11,834,508 COVID-19 tests have been performed in the US resulting in 1,523,534 (12.9%) confirmed cases [1]. The actual number of infected Americans is much larger. Antibody seroprevalence testing in Los Angeles County , California, estimates those infected around 4.65% implying actual infection is about 43-fold larger than confirmed cases [2]. Another study concluded that undiagnosed COVID cases represent the infection source of 79% of documented cases [3]. Accurate testing will be crucial to controlling and understanding this pandemic. Estimation relies on testing kit accuracy (sensitivity/specificity). Low sensitivity will underestimate disease prevalence, while low specificity will overestimate [2].

Testing comes in two broad types, testing for nasopharyngeal viral RNA and serologic testing for antibodies, which occur in response to the disease. RNA testing is done with polymerase chain reaction (PCR) is cost-effective, easy to perform, and now available [4]. However, the PCR test has accuracy issues. Sensitivity of FDA-approved viral RNA tests range from 63%–95% (Table 1) [5-8]. Sensitivity of RNA tests is dependent on the site of specimen collection. Sensitivity was highest in bronchioalveolar lavage (93%), then sputum (73%), nasal swab (63%), feces (29%) and blood (1%) [5]. Another study found that patients with pneumonia often have negative nasopharyngeal samples, but positive lower airway samples [9]. The sensitivity of PCR tests have been estimated at 71%, resulting in ~30% of infected patients having a negative finding. Another drawback is the presence of viral RNA does not mean the virus is live, therefore, detection does not necessarily mean the virus can be transmitted [9]. RNA-based tests are limited to the setting of acute illness. Saliva-based tests offer promising results as a non-invasive and non-aerosol generating method of specimen collection [10]. Compared to nasopharyngeal tests, saliva specimens have high sensitivity (84.2% [10]) and can be self-administered [10]. Another study reported that SARS-CoV-2 viral load in posterior oropharyngeal saliva samples was higher at initial presentation of COVID-19 symptomatic patients, increased with age, presence of comorbidities, and severity of the COVID-19 disease [11]. Reduced variability in samples taken from self-administered tests is helpful for mass testing because it preserves collection reliability and allows patients to send in their own samples from the comfort of their home.

The second type of test is serologic, which detects immunoglobulins (IgG and IgM) specific for SARS-CoV-2 and provides an estimation of population virus exposure [4]. One drawback of serologic testing is the lag period between symptoms and antibody formation-one analysis found patients do not begin to seroconvert until 11–12 days post-symptom onset [12].The sensitivity and specificity of FDA-approved serologic tests ranges from 61.1%–98% and 90%–100% [13]. Many FDA-approved serologic tests have high sensitivity and specificity. For example, Cellex Inc. developed a rapid diagnostic test with 93.8% sensitivity and 95.6% specificity. Bio-Rad manufactured an ELISA test with sensitivity and specificity of 98% and 99%, respectively (Table 1) [13].

There are also clinical associations with confirmed COVID-19 patients. An analysis of 119 patients with COVID-19 at from Wuhan University revealed an association with low urine specific gravity and increased pH [14]. In addition, the urine glucose and proteinuria correlated with severe/critical cases compared to mild/moderate [4]. The results imply that certain urinalysis profiles can be used to predict the severity of disease and possibly testing of asymptomatic patients that could be quarantined until a definitive test can be completed [14].

To address the development of a reliable test, the Department of Health & Human Services (HHS) provided funding for the development of Simplexa COVID-19 Direct Assay and to QIAGEN to accelerate development of their RPS2 test [15]. Additionally, HHS is purchasing the ID NOW COVID-19 rapid point-of-care test (Abbott Diagnostics Scarborough Inc.) for public health labs (Table 1) [16]. The FDA is issuing Emergency Use Authorizations to expedite distribution [17]. States have differing amounts of laboratories authorized for testing (Fig. 1). The targeted distribution of tests to areas of high density (Fig. 1–black diamonds) is paramount to ensure that resources are not undersupplied.

The road back to normalcy is contingent on accurate tests, allowing suppression of spread. When a localized outbreak occurs, it will be important to have reliable testing methods to promptly contain it. Random serologic testing can be used to surveil populations at high-risk for an outbreak. PCR tests can be used to assess those with active infection who may be asymptomatic.

Targeted distribution of tests needs to be to areas where COVID is more prevalent and where people are at higher risk. In addition to distribution, the quality of the tests requires improvement. Many prospective tests in development report promising results in under 60 min, such as Mammoth Bioscience's CRISPR-based lateral flow assay (sensitivity:90%, specificity:100%) and United Biomedical's kit (sensitivity:100%, specificity:100%) (Table 1) [13,18].

In the present era, technology allows diagnostics to be readily available. Understanding the current disease state in communities' plays a role in the acceptance of control measures that require individual actions. Now is the time to ensure systematic and coordinated efforts between the clinical, commercial and public sectors to leverage the power of testing to address the pandemic at our door.

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Table 1
Overview of COVID-19 FDA approved/non-FDA approved diagnostic tests.

COVID-19 diagnostic tests				
Authors/company	Country	Type of test	Sensitivity & specificity	Development phase
Tests approved for use in the United States				
Cellex Inc.	US/China	Rapid Diagnostic Test	Sensitivity: 93.8% Specificity: 95.6%	Approved by FDA for EUA; CE approval
Diasorin Inc.	USA	ELISA	Sensitivity: 90–97% Specificity: 98%	Approved by FDA for EUA
Bio-Rad	USA	Modified ELISA	Sensitivity: 98% Specificity: 99%	Received EUA
Roche	US/Switzerland	Electro-chemiluminescence immunoassay (ECLIA)	Sensitivity: 65–100% Specificity: 99.81%	Received EUA, available for purchase by healthcare professionals and researchers.
Euroimmun AG	Germany	ELISA	Sensitivity: 61.1–90% Specificity:100%	Received EUA, available for purchase by healthcare professionals and researchers.
Diacarta	US	Quantifier SARS-CoV-2 Multiplex Test Kit	Sensitivity: 95% Specificity: 100%	EUA
InBios	US	Smart *Detec* SARS-CoV-2 rRT-PCR Kit	Sensitivity: 100% Specificity: 96.7%	EUA
Gnomegan	US	COVID-19 RT-Digital PCR Detection Kit	Sensitivity: 100% Specificity: 100%	EUA
Simplexa COVID-19 Direct	US	COVID-19 RT-Digital PCR Detection Kit	Sensitivity: 100% Specificity: 100%	EUA
QIASTAT-DX	US	COVID-19 RT-Digital PCR Detection Kit	Sensitivity: 85.1–98.1 Specificity: 99.2–100	EUA
Tests approved for diagnostic use in other countries				
Aytu Biosciences/Orient Gene Biotech	US/China	RDT, solid phase immunochromatographic assay	Sensitivity: 87.9% (IgM) and 97.2% (IgG) Specificity: 100% for IgM and IgG	CE approved, used in China in clinical settings, awaiting FDA approval
ScanWell Health/INNOVITA	US/China	Proprietary	Sensitivity: 87.3% Specificity: 100%	Cleared by China's National Medical Products Administration (NMPA), and pending approval by US FDA
Quotient	Switzerland	MIRA - Multiplexed Immuno-Refractive Assay	Sensitivity: 100% Specificity: 99.8%	Currently available in Europe
Liming Bio	China	RDT (colloidal gold lateral flow assay)	Sensitivity: 62% (IgM) Specificity: 100% (IgM)	CE/IVD
Tests in development				
Broughton et al. (Mammoth Biosciences)	US	CRISPR-based lateral flow assay	Sensitivity: 90% Specificity: 100%	Pre-clinical
United Biomedical (UBI)/c19	US	Proprietary	Sensitivity: 100% Specificity: 100%	In testing in San Miguel, CO
Coris Bioconcept	Belgium	Dipstick (lateral flow assay)	Sensitivity: 60% Specificity: 99%	Clinically testing
Ma et al.	China	Chemiluminescent immunoassay	Sensitivity: 98.6% Specificity: 92.3–99.8%	Pre-clinical

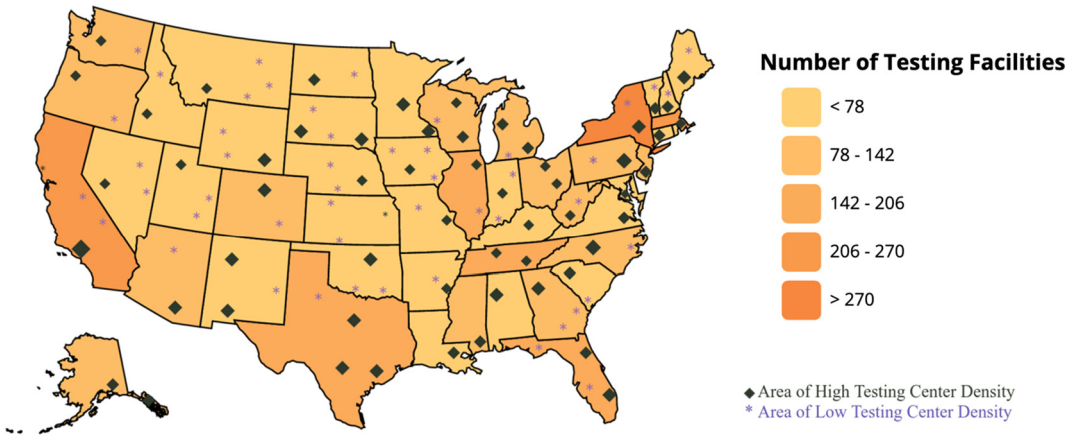

Fig. 1. COVID-19 laboratory facilities across the United States (US). Areas of the US with a high density of testing centers are labeled with a diamond, whereas areas with a low density of testing centers are marked by asterisks.
*Source: COVID-19 Testing Sites Locator. Arcgis. https://www.arcgis.com/apps/webappviewer/index.html?id=2ec47819f57c40598a4eaf45bf9e0d16

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