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Pragmatic Approach to the Use of Current and Novel Diagnostics to Support the COVID-19 Pandemic Response

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Executive Summary

The novel coronavirus, SARS-CoV-2, emerged and rapidly spread worldwide in early 2020, causing the second pandemic of the 21st century. Public health authorities and experts quickly determined that broadly available testing was critical to diagnose infections and contain the spread of the disease known as COVID-19. In the United States, at the start of the outbreak, a lack of test diversity and related supply constraints limited testing capacity.

Currently, several new testing approaches and diagnostic modalities are being developed, which use novel supply chains. These alternatives have the potential to alleviate some bottlenecks across the testing spectrum and expand all testing capacity to achieve public health goals.

The introduction of new technologies provides an opportunity to think about a practical approach to the deployment of the testing. In an ideal situation, where testing is equally accurate and all supplies are readily available, consideration of which tests are most appropriate for each environment would not be necessary. However, given the current capacity limitations, some broad principles should be applied when considering how to deploy available testing most effectively.

In general, if tests with varying test performance (i.e., sensitivity and specificity) have to be prioritized for certain use cases, tests with the greatest sensitivity should be prioritized for symptomatic and exposed persons in settings with vulnerable populations and high likelihood of disease spread. Tests with lower sensitivity can be used for asymptomatic screening. If these lower sensitivity tests will be deployed in settings with high likelihood for disease spread, the test should be repeated often. Point of care and rapid turnaround testing should be used whenever possible, taking into account the fact that diagnostic testing should be done with highly sensitive assays.

A thoughtful and practical approach to testing will help better contain the spread of SARS-CoV-2, especially when coupled with isolation and quarantine. Authorities making decisions about testing strategies and the allocation of testing resources should consider these principles in their decision-making.

Background

In a matter of months, SARS-CoV-2, the virus that causes COVID-19, spread around the world resulting in a pandemic. From the outset, public health and academic experts stated that diagnostic testing and isolation of ill persons, plus quarantine of exposed persons, were critical to control the spread of the virus.[1, 2] During the first six months of the pandemic, the main diagnostic modality was reverse

transcriptase polymerase chain reaction (RT-PCR), due to its widespread availability and its sensitivity to and specificity[1] for identifying the virus. In the United States, however, constraints in RT-PCR supplies and laboratory capacity, confusion about changing regulatory requirements, and poor performance assays have hindered the ability to conduct widespread testing. This reduced our ability to control the spread of the virus.

U.S. testing capability and capacity has grown since the start of the pandemic but continues to fall short of the approximately 2.5 million diagnostic tests per day that some experts suggest are needed to effectively control the spread of COVID-19.[2] In April, there were roughly 750,000 diagnostic tests being done per week by clinical, commercial, and public health laboratories, which grew to a peak of around 2.5 million tests per week by the middle of July. Testing, however, still relies primarily upon RT-PCR.[3]

Challenges with RT-PCR-based testing

While RT-PCR offers high sensitivity and specificity with a well-collected and preserved clinical specimen, it has several limitations. These limitations include the following:

- Tests must be performed in a high-complexity laboratory with Clinical Laboratory Improvement Amendments of 1988 (CLIA) certification.
- Until recently, these tests required the use of supply-limited nasopharyngeal swabs.
- Transportation of the samples to the laboratory has played a role in testing delays. For example, if collected samples need to be shipped to a distant CLIA-certified laboratory (e.g., commercial laboratories), final results can be delayed for more than 48 hours, after which time laboratory confirmation of a case is less actionable. (This lack of timeliness is less of an issue for clinical laboratories, where samples are typically collected in and transported to a laboratory in the same location.

Alternative approaches to testing

Since the pandemic began, some of the technological advances in the diagnostic testing space include the development of isothermal amplification assays, which are similar to RT-PCR assays in that they amplify nucleic acid, can be deployed as point-of-care (POC) tests and provide results in less than 30 minutes. However, two such assay platforms that have been launched to-date and that received Food and Drug Administration (FDA) Emergency Use Authorization (EUA)[4] have had problems with sensitivity.[5] Another diagnostic modality is antigen testing, which also can be deployed as a POC test and provide results in less than 30 minutes. Antigen testing has also been associated with lower sensitivity, limiting its deployment for diagnostic testing. As of the middle of August, there were three antigen tests available with FDA EUA with limited throughput. At of the end of August, another test with FDA EUA was added, which has high throughput potential. [4]

The primary focus to date has been on diagnostic testing of symptomatic or exposed persons, however, asymptomatic screening and surveillance testing are two other important testing pathways that have gained traction in recent months. Asymptomatic screening is for individuals not suspected to have (or

[1] Sensitivity refers to a test's ability to detect cases of the disease among persons with the disease, and specificity refers to test's ability to rule-out cases of the disease in persons who do not have the disease.

have had contact with known cases of) COVID-19 and can use the same types of testing modalities and approaches that are used for diagnostic testing.

Note: Although outside the scope of this paper, surveillance testing (e.g. wastewater surveillance) which is population-level testing that can be done at points in time to answer questions such as overall disease burden, can also use the same testing modalities and approaches.

Investing in innovations to increase speed, convenience, and throughput

To address some of the challenges in the diagnostic testing space related to the lack of novel, scalable diagnostic modalities and especially the reliance on RT-PCR, the National Institutes of Health (NIH) launched the Rapid Acceleration of Diagnostics (RADx) Initiative. This initiative aims to accelerate the development, commercialization, and implementation of innovative technologies for COVID-19 testing. [6] The new technologies being scaled by the RADx Initiative hold the promise of alleviating supply and capacity constraints, while also potentially providing benefits in terms of easier sample collection and faster testing times. With these initiatives, testing capacity is projected to rise to 2.7 million tests per day by the end of 2020. [6]

Simultaneously, clinical, commercial, and public health laboratories have been investigating novel strategies of their own, as have other laboratory assay manufacturers. Their approaches also have the potential to both alleviate supply and capacity constraints and provide benefits in terms of easier sample collection and faster testing times.

Novel Technologies and Enhanced Approaches

Some of the most relevant technologies funded by the RADx Initiative include Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), microfluidics technology, and next generation sequencing (NGS) to detect SARS-CoV-2. Where applicable, these efforts are fast-tracked for EUA by the FDA.

Some of the enhanced approaches to testing include pooling samples for RT-PCR, self-collection of samples at home, and tests using saliva samples. While other technologies and approaches are being developed, for the purposes of this analysis we focused on novel technologies that received financial support from the RADx Initiative, as they are likely to be deployed near-term and are expected to rapidly scale testing by the end of 2020. [7]

Novel Technologies

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)

CRISPR is a technology that uses a piece of RNA to locate a gene of interest that is present in the RNA of the SARS-CoV-2 virus, which then is snipped out by enzymatic molecular scissors (e.g., Cas9), generating a fluorescent signal that indicates the presence of the virus. The technology can be deployed as a POC or laboratory test and, in the case of the POC test, can offer results in less than 30 minutes. One RADx-funded CRISPR assay is performed on a handheld device that is fully-disposable. Another is performed in high-complexity CLIA-certified laboratories. Both use nasal swab samples but at least one is evaluating using saliva as well.

Microfluidics

Microfluidics is a technology that uses a chip to detect proteins in the blood. One such application being supported by the RADx Initiative is the use of microfluidic technology to detect SARS-CoV-2 by real-time RT-PCR on a high-throughput platform, using saliva samples. This technology increases sensitivity and enables processing with small amounts of sample. Microfluidics are expected to increase throughput and decrease turnaround times, particularly in large commercial laboratories.

Next Generation Sequencing (NGS)

Diagnostic NGS allows for the molecular detection of genetic sequences of SARS-CoV-2, providing not only a diagnostic test, but also a genomic sequence that can be used to monitor genetic changes in the virus over time. NGS is performed on high-throughput platforms and can process thousands of samples with a high level of accuracy. Two RADx-funded projects will significantly expand rapid testing on existing NGS platforms in CLIA-certified laboratories, using nasal or saliva samples.

Enhanced Approaches

Pooling of Samples for RT-PCR

Traditionally, with RT-PCR testing, each clinical sample is tested individually. Another possibility being considered is pool testing. For example, in areas with a low prevalence of SARS-CoV-2, users can pool multiple samples together for RT-PCR to identify whether there are any positives within the group. If there are, users test individuals within the pool. This strategy can be deployed to conserve some RT-PCR reagents. In low SARS-CoV-2 prevalence settings, most pools are expected to be negative and, hence, a second step of testing individual samples is not likely to be needed. When samples are pooled together, however, there is a potential loss of sensitivity of the assay to detect the virus, so the FDA recommends pools of no more than four to five samples. There are currently at least two EUAs for pooled RT-PCR testing for detection of SARS-CoV-2.

Self-Collection of Samples at Home

Historically, clinician-collected samples were used to detect viral respiratory pathogens. During this pandemic, however, the concept of a self-collected sample at home has gained traction as it eliminates some access-barriers, such as having to travel to a location to be tested or having to wait in a line to be tested. This approach would also preserve resource-limited personal protective equipment (PPE), which clinicians must wear when collecting samples. There are currently at least two EUAs for at-home sample collection.

Saliva Samples

Historically, respiratory tract samples, especially nasopharyngeal (NP) and oropharyngeal (OP) samples, were used to detect viral respiratory pathogens. The rapid spread of SARS-CoV-2 created supply chain shortages in NP and OP swabs, as well as in the transport media for storing swabs before testing. These shortages limited the amount of testing that could be done. Recently, however, saliva samples have been successfully used with RT-PCR to detect SARS-CoV-2. Using saliva rather than NP and OP samples decreases the likelihood of swab and transport media shortages. Also, saliva-based testing might increase the willingness of people to be tested, since the sample collection process is not invasive.

Advantages and Disadvantages of Novel Technologies and Enhanced Approaches

This paper outlines six novel technologies or enhanced approaches. There are advantages and disadvantages to the use of any of these. To compare and contrast the technologies, it is useful to consider the supply chains used for each, the turn-round time to obtain the test result, the ability to scale the testing, the invasiveness of the sample collection process, and the dependency on a clinician to collect the sample. Table 1 provides a comparison of the technologies and approaches using these variables.

Table 1: Comparison of Novel Technologies and Enhanced Approaches

	Supply chain	Type of laboratory for testing	Time to receive results	Invasiveness of sample collection	Clinician dependency for sample collection
Novel Technologies					
CRISPR	Nasal swabs; no swabs	POC and CLIA high-complexity laboratory	30 minutes; 2-3 days*	Low to medium	Varies
Microfluidic RT-PCR	NP and OP swabs	CLIA high-complexity labs	2-3 days*	Medium	Yes
NGS	Nasal swabs	CLIA high-complexity laboratory	2-3 days*	Medium	Yes
Enhanced Approaches					
Pooled RT-PCR Testing§	Nasal, NP, and OP swabs	CLIA high-complexity laboratory	1-3 days*	Medium	Yes
Saliva Samples†	No swabs	CLIA high-complexity laboratory	N/A	Low	No
At-Home Collection§	Nasal swabs; no swabs	CLIA high-complexity laboratory	N/A	Low to medium	Varies

* The sample preparation and testing can be done in less than one day, but in the case of commercial laboratories, the process of transporting the sample to the laboratory and reporting the results adds additional time to the process; with high-throughput platforms more samples can be tested in the same amount of time.

† EUAs have been granted for saliva-based sample collection and testing by RT-PCR.

§ EUAs have been granted for saliva-based and nasal sample collection and testing by RT-PCR.

Best Practices for Deployment of Testing

In an ideal situation, where testing is equally accurate and all supplies are readily available, consideration of which tests are most appropriate for each environment would not be necessary.

However, given the current capacity limitations, some broad principles should be applied when considering how to deploy available testing most effectively.

To match testing technology and strategy to the testing objective and environment, it is useful to consider three variables: medical necessity for testing, the vulnerability of a population to severe disease, and the affected's potential to infect others.

Table 2: Factors to Consider in Deployment of Testing

Environments		Medical Necessity	Vulnerability to Severe Disease	Spreading Potential
In-patient Facility		High	High	Low
Out-patient Facility		High	Medium/High	Low
Group / Institutional Setting				
	Nursing Home	High	High	High***
	Correctional Facility	Low	Low/Medium	High
School Setting				
	University (on-campus housing)	Low	Low*	High
	Commuter School	Low	Low*	Medium
	K-12	Low	Low*	Medium**
	Daycare & Pre-school	Low	Low*	Medium**
Athletic Team				
	Professional, Collegiate & Youth Sports	Low	Low*	High
Close-quarter workplaces		Low	Medium/Low	Medium
Office workplaces		Low	Medium/Low	High

*These environments will have persons at higher risk, but the majority are likely to be lower risk, based on the typical age of persons in this environment.
**The role of children in disease-spread is not well-defined.
*** With appropriate, consistent use of personal protective equipment (PPE), spread should be low; however, to date, these environments have had difficulty controlling the spread of the virus within their facilities.

Applying Environmental Factors to Testing Priority and Test Attributes

In general, if tests with varying test parameters (i.e., sensitivity and specificity) have to be prioritized for use, tests with the greatest sensitivity should be prioritized for symptomatic and exposed persons in settings with vulnerable populations and high likelihood of disease spread.

Tests with lower sensitivity can be used for asymptomatic screening. If these lower sensitivity tests will be deployed in settings with high likelihood for disease spread, the test should be repeated often. Point of care testing should be used whenever possible, taking into account the fact that diagnostic testing should be done with highly sensitive assays.

Conclusion

In conclusion, significant supply chain issues have limited testing capacity and inhibited the United States' ability to test people as broadly and frequently as is necessary, given the transmission dynamics of this novel virus. These dynamics require continuous reassessment of testing capabilities and modalities to optimize their benefits and limit disease spread.

Laboratories and manufacturers are rapidly innovating to close the testing capacity gap. A sensible approach to allocating available testing to appropriate environments will help to ensure progress toward a sustained balance of public health and resumed activity.

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