SARS-COV-2 USE CASES WHITE PAPER

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INTRODUCTION

The COVID-19 pandemic is now nearly eight months old, and far from over. The global healthcare community has mounted an unprecedented response with scores of vaccine development programs, over 1,000 antiviral drug clinical trials in progress, and the introduction of over 1,200 SARS-CoV-2 infection-related medical tests at the time of writing. There are many applications for the SARS-CoV-2 tests, some of which are served well, while others are wanting.

This white paper is a component of a larger project involving the Rockefeller Foundation, Arizona State University and Duke University to develop SARS-CoV-2 testing protocols for a wide range of the US population in order to continue safely reopening our society. The testing protocols will be designed for workplace, school, and community settings. The project goals involve creating an evidence-based framework with expert guidance for the effective and feasible use of the appropriate tests. In order to lay the groundwork for the project, the description of testing use cases, use settings, and target product profiles are required.

In this white paper, use cases for SARS-CoV-2 testing are described and assessed. There are many definitions for use cases. In this paper the following definition is used:[1] "a use case is a description of all the ways that an end-user wants to use a system." In this paper the "system" is a SARS-CoV-2 medical test. With this definition in mind, nine use cases for SARS-CoV-2 tests are listed: **triage** testing, **confirmation** of triage testing, **diagnosis** and **differential diagnosis** of symptomatic individuals, determination of **previous exposure**, population **surveillance**, **environmental testing**, **health checks and surveys**, and **screening** of non-symptomatic individuals (see Table 1). Triage testing is not currently available, but as described in this paper, could have a significant impact on effective testing protocols. Diagnosis using RNA tests is the most substantial form of testing today, while differential diagnostic testing with the addition of flu A and B is emerging. Determination of previous SARS-CoV-2 exposure with antibody tests is popular but complicated by what the results actually mean with regard to patient management. Population surveillance with RNA and antibody tests continues to inform the epidemiology community about incidence and prevalence of COVID-19. Environmental testing can be employed to determine the effectiveness of cleaning protocols to rid common spaces of viral contamination, whereas health checks and surveys are employed to assess the risk of infection in individuals or groups. There is a surge in the screening of non-symptomatic (asymptomatic/pre-symptomatic) people to determine existing and previous infections. There are several other use cases not listed here. For more details please see www.halteresassociates.com.

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In this white paper, there is a focus upon three high profile use cases: **diagnosis** in symptomatic individuals, **previous exposure** determination, and **screening** of non-symptomatic individuals. Diagnosis is the most common form of testing today, previous exposure determination is the most controversial, and non-symptomatic screening is essential for safely reopening the economy. The use case descriptions include: the intended use, types of tests available, populations to be tested, use settings for testing, and general requirements for tests. In addition, there are assessments of the status of testing and unmet needs, as well as near- and mid-term test improvements under development by the diagnostic laboratory and manufacturing communities.

An understanding of the SARS-CoV-2 testing use cases and use settings sets the stage for the development of target product profiles that are useful, not just for the development of tests by manufacturers, but for the assessment of tests on the market for specific applications by purchasers and users of the tests. With so many tests available for SARS-CoV-2—RNA, antibody, and antigen detection—with very different performance characteristics, it can seem overwhelming to determine which tests will provide the specifications absolutely required to satisfy the testing need. For example, the screening use case addresses many of the factors that need to be considered to develop testing protocols for priority settings of the Rockefeller Foundation project. In some cases, the tests used for diagnosis and previous exposure can play a part in screening of non-symptomatic persons. It is hoped that this white paper will help a variety of healthcare stakeholders to understand the applications, status, issues, and potential solutions to SARS-CoV-2 testing. Target product profiles and testing protocols will be the subject of future communications.

Use Case	Intended Use
Triage	Intended use is to determine if a symptomatic individual has a reasonable likelihood of a current SARS-COV-2 virus infection warranting temporary isolation pending confirmatory testing
Confirmation of triage tests	The intended use is to confirm that an individual is currently infected with SARS-CoV-2 virus after triage testing
Diagnosis in symptomatic individuals	The intended use is to diagnose a symptomatic individual with a SARS CoV-2 infection
Differential diagnosis in symptomatic individuals	The intended use is to diagnose an individual with influenza like illness (e.g., Flu A, Flu B, RSV, SARS-CoV-2) and febrile diseases with COVID-19-like symptoms
Previous exposure determination	Intended for use to determine if an individual without symptoms has previously been exposed to SARS-CoV-2 virus
Surveillance	Intended use is to monitor a local or sentinel population for one of three purposes: 1) the estimation of incidence of current SARS-CoV-2 infection in symptomatic persons 2) the estimation of incidence of current SARS-CoV-2 infection in asymptomatic and pre-symptomatic persons 3) the estimation of prevalence of SARS-CoV-2 infection based upon prior exposure to SARS-CoV-2 (cumulative or changes over time)

Use Case	Intended Use
Environmental monitoring	The intended use is to monitor for the presence of SARS-CoV-2 virus on surfaces, in the air, in commercial vehicles, in latrines, or other sites of interest
Health checks and surveys for non-symptomatic individuals (asymptomatic/pre-symptomatic)	The intended use is to screen all employees and visitors to a workplace or similar environment for symptoms or other risk factors for existing or future SARS-CoV-2 infection
Screening of non-symptomatic individuals (asymptomatic/pre-symptomatic)	There are two intended uses: 1) determine if an asymptomatic or pre-symptomatic individual has a current SARS-CoV-2 infection 2) determine if an individual has been previously exposed and is likely to have immunity.

Table 1: List of use cases and intended uses

DIAGNOSIS IN SYMPTOMATIC INDIVIDUALS

The intended use: To diagnose an active SARS CoV-2 infection in an individual with symptoms.

Types of tests: Today, testing is mostly for viral genomic RNA by PCR or other nucleic acid amplification technologies, although a number of viral antigen tests are available or under development.

Populations to be tested: Testing is primarily conducted in persons with respiratory disease symptoms and typically with a physician's prescription. In some locations, asymptomatic persons meeting certain risk criteria are permitted to be tested (e.g., New York, Texas, Washington State) while other locations are slowly opening testing to all individuals interested in being tested (e.g., South Carolina, Georgia)

Use settings: Testing sites include locations where individuals commonly seek primary care, such as emergency rooms, urgent care clinics, hospitals, and primary healthcare facilities or where individuals are referred for advanced care. However, concerns about infecting others present at the site of presentation have driven many healthcare systems to provide specific places where individuals suspected to have COVID-19 are asked to go. It is also common for symptomatic individuals to be sampled from their car window while waiting in line in a parking lot by a properly protected healthcare professional. Samples are properly contained and are sent to testing sites.

Most testing is conducted in large national labs, but decentralized testing using a number of testing systems available from vendors with smaller instruments and lower throughput are expanding to more sites (e.g., hospitals, primary care clinics, urgent care clinics) as the vendors can provide tests and instruments. In many states public health labs offer surge support by testing overflow samples from the county health systems that they serve.

Utilizing SARS-CoV-2 viral antigen tests with sufficient performance, such as simple lateral flow devices, should expand testing sites to small clinics or the home. Substantial sample self-collection of saliva cups/tubes or nasal swabs at an individual's home is now occurring with EUA kits that include provisions for pickup or by mail into clinical labs.

The general requirements for test performance: Sensitivity needs to be quite high, preferably > 99%. A false negative result, particularly in at-risk populations (e.g., the elderly, persons with pre-existing conditions, or immuno-compromised individuals), could result in an increased morbidity and mortality rate, while also increasing the risk to medical personnel and increasing overall SARS-CoV-2 transmission. Although false positives are less problematic, poor specificity could lead to unnecessary and costly isolation or hospitalization under quarantine and loss of work time. Also, healthcare personnel might be forced to wear PPE when it is not needed. Cross-reactivity with other respiratory and febrile disease pathogens such as the four coronaviruses associated with the common cold would be highly problematic.

Status of testing, unmet needs: Recent estimates from Harvard University suggest that there are over 300K tests performed per day in the US. The Rockefeller Foundation RNA testing expansion plan calls for developing state-specific plans to expand overall US testing from 1M/day to 3M/day, then 30M/day. This scale-up will likely require substantially more central lab testing but will also require more decentralized testing. Time to result is problematic. It can take 3-13 days for a result to be reported from samples sent out to off-site labs.

Recent interviews with several clinical lab directors indicated that many labs have implemented three to six testing platforms in order to maintain testing volumes when testing supplies run low for one or another platform. Without this flexibility, they fear the possibility of diminished testing capacity for prolonged periods. With the push to scale testing even further, many of the labs continue to look at options to bring in additional test platforms that can process more samples per shift. In addition, the labs find that the supply of sample collection devices, PPE, and other materials are persistent problems.

At the height of the infections in New York City, the RNA tests were positive in only about 25% of the cases. Most other testing sites have substantially lower test positive rates of 5% or below. A recent investigation showed fewer than 0.2% positivity in parts of South Carolina. Developing means of targeting testing to those people who are more likely to be positive could improve test utilization and costs (e.g., health surveys, triage testing). Serological surveillance can help to establish prevalence in specific locales (e.g., neighborhoods, cities, counties) to better target testing and public health interventions. On the other hand, there is a trend toward testing more non-symptomatic persons who may have been exposed to infected individuals.

Near-term improvements: Beyond expanding testing as currently performed, there are a variety of considerations to improve the use of the RNA testing capacity. One is to pool samples (four or more samples combined and tested by one test) in much the way pooling has been deployed for volunteer blood donor screening. Although decreased costs and the need for fewer tests are attractive, the impact of the potentially decreased lower limit of detection per sample will need careful study. Reports of the use of pooling protocols and the associated concerns have already appeared. Recently, the FDA issued guidelines for pooling SARS-CoV-2 samples for RNA testing.

There are issues concerning the quality of the existing RNA tests. There have been reports of false negative results due to poor sampling (e.g., relative accuracy and reproducibility of oral fluid or nasopharyngeal (NP), mid-turbinate (MT) and nasal swab sampling methods) or poor test design (e.g., poor limit of detection, primer/probe design). These issues are not surprising in the early phases of new infectious disease outbreaks and will likely be worked through with time in the laboratory community. Clinical labs continue to do a great deal of validation of methods and protocols. There is a substantial push to move away from NP swabs to MT

swabs and saliva due to lack of availability of NP swabs, the difficulty of NP sample collection (e.g., training of healthcare professionals, discomfort to patient), and health risks to medical personnel in PPE collecting the samples. Recent studies indicate that MT swabs, which can be self-collected, have similar performance to NP swabs. Saliva has been the subject of several studies but appear to perform best in patients with relatively high viral loads.

The lack of accepted gold standards and high-quality validation sample panels has been a limiting factor to date. The availability of validation sample sets from FDA and NCI is a major step in the right direction. However, the establishment of a nationally accepted gold standard assay will have a substantial impact on the evaluation of existing and future tests.

As the cooler temperatures of the fall and winter seasons arrive in North America, the number of persons with respiratory symptoms in the US will rise substantially as the flu season begins. Expanding testing to include flu A/B and possibly other respiratory pathogens will be valuable (see Table 1, differential diagnosis). Several test vendors have either already announced test availability or plans to develop them. The CDC recently received EUA for a PCR test for flu A/B and SARS-CoV-2. In the elderly, especially in nursing home populations, RSV infection is associated with high mortality and sepsis-like presentations, much like for COVID-19. RSV may need to be included for syndromic testing of the very young and very old.

There have been numerous reports of SARS-CoV-2 RNA tests remaining positive in confirmed cases of COVID-19 for many days or weeks after symptoms have ceased. There is a general correlation of low viral load late in infection (e.g., high “Ct” in PCR tests) and an inability to culture SARS-CoV-2 from these samples, suggesting that many of the people with lingering RNA might not be infectious. In support, there are reports that sub-genomic viral RNA, associated with active viral replication in cells, is less common in samples weeks after the initiation of symptoms. Tests that can differentiate infectious versus non-infectious viral nucleic acid are needed and under development.

Mid-term improvements: In addition to pooling samples, there is the possibility of decreasing the number of RNA tests used on samples from persons with influenza-like illness (ILI) that is not COVID-19. This could be achieved if triage testing (see Table 1) could be implemented with high sensitivity (~99%) and adequate specificity (>50%). Simple, fast, inexpensive point of care triage tests could be devised. Some triage tests are under investigation based upon rapid analysis of blood cell morphology or volatile organics in breath. Also, well-designed and clinically tested triage questionnaires have been used in other disease states (e.g., volunteer blood donor testing, type 2 diabetes risk, multiple myeloma risk).

Numerous studies have appeared concerning the use of a variety of biomarkers beyond SARS-CoV-2 RNA, antibodies, and antigens to supplement the information concerning COVID-19 including blood cell counts, cytokines (e.g., IL-6), troponin, CRP, and other host response markers. It is possible that some combination of host response tests could be used to diagnose and manage COVID-19 in patients with undetectable RNA early or late in the disease. This could help to reclassify “asymptomatic” persons to new classes of “symptomatic.”

PREVIOUS EXPOSURE DETERMINATION

The intended use: To determine if an individual without current symptoms has previously been exposed to SARS-CoV-2. Pending sufficient supporting data (see below), detection of previous exposure could be an indication of at least temporary immunity. It will be important to also know that the individual is not currently infected. Potentially, such an individual would not require isolation and could associate with uninfected or infected individuals with minimal danger of transmission or new infection. However, there will need to be substantial supporting data to obtain such a claim from the FDA.

Populations to be tested: Persons that have been ill with respiratory symptoms are candidates, whether they recovered at home or were hospitalized. People could learn of their antibody status if they participated in population surveillance studies (Table 1). Many people in the general population want to know their status since they might have been infected yet were asymptomatic, especially those who may have been at higher risk of exposure to infected individuals.

Assuming that tests can be shown to correlate with immunity to SARS-CoV-2 infection, it could be possible for such people to continue in existing jobs with little PPE (e.g., nurse, school teacher, assisted living facility employee, first responder) or to take on new jobs because of their protected status (e.g., food handler, hospital worker). This approach has been followed successfully in other epidemics such as the West African Ebola outbreak in 2014.

Use settings: Most testing is conducted in large clinical labs. In contrast to diagnostic testing, which is mostly performed on symptomatic persons, previous exposure testing is conducted in persons without current symptoms. As a result, the individual to be tested will tend to present in places of primary healthcare or other convenient locations and will not require a rapid result for most purposes. Blood samples can be collected in primary healthcare facilities including pharmacy clinics and at home, then shipped to an off-site lab. If simple point-of-care devices are employed, testing can be conducted at the site of presentation. Self-testing has been reported, but so far test performance has been problematic.

General requirements of testing: The available serology tests use SARS-CoV-2 virus-specific IgA, IgM and/or IgG antibody detection assays. At this time IgG is the preferred immunoglobulin due to longer-term (at least weeks) of detection versus IgA and IgM. The rise of IgG antibody titers may lag the appearance of IgA or IgM titers, although there have been reports of IgG seroconversion before IgM. As a result, the interpretation of IgM positivity is currently controversial. Multiple SARS-CoV-2 proteins and protein segments are commercially available for test developers, including viral surface spike and nucleocapsid proteins. Most tests are qualitative; however, it could be useful to measure blood antibody levels to increase confidence in true positive samples (signal versus cutoff) or to measure changes in titer over time.

Assuming a correlation of a positive result with immunity, a false negative result could prevent a person from freely interacting with others under conditions that require less PPE than for others who are not immune. Although disappointing, the result is not life threatening. A false positive result is more problematic in that it could give the tested person a false sense of protection leading to behavior potentially risky to the tested individual and to others. Therefore, high specificity, 99% or greater, is highly recommended.

Based upon the continued presence of SARS-CoV-2 RNA in clinical samples late in the infection, some people that are IgG positive could still be infectious. As a result, IgG positive persons might, in some cases, require an RNA test to confirm clearance. It is worth noting again that some viral culture studies of patient samples have shown that RNA late in an infection might not be associated with infectious material, especially when there is a low viral load.

Status of testing, unmet needs: Several manufactures have introduced IgG tests on large laboratory immunoassay platforms. Most of these tests claim high sensitivity and specificity. A very large number of lower throughput tests have been reported, often in a lateral flow format. Surprisingly, many appeared as early as January 2020. Reports suggest that many of these very early tests were relabeled SARS-CoV-1 tests. Over the last several weeks, the FDA has removed more than 50 immunoassays from the market due to performance and other concerns.

There are two major issues with SARS-CoV-2 serology tests. The first is the number of false positive results. The performance of any test is dependent upon the pre-test probability of obtaining a true positive or negative result, which is dependent upon prevalence. With an immunoassay that has 99% specificity, in a 1% SARS-CoV-2 prevalence (common in the US) setting there would be one false positive result for every true positive result. If the results will be used to tell an individual that they have been exposed to SARS-CoV-2, this would be true only 50% of the time. Alternatively, if the assay has a specificity of only 90% in the same 1% SARS-CoV-2 prevalence setting, there would be 10 false positives for every one true positive. In this situation, the test would be true less than 10% of the time. Some existing tests have reported specificity of 100%, but there is a concern about whether or not the manufacturers tested enough negative samples to justify the claim; some may have, some may not have. For donor blood screening, where false positive results historically are a major concern, typically at least 10,000 negative samples would be tested. From a study of SARS-CoV-2 antibody test product inserts, none of the commercial tests have been run with that many samples to establish their performance claims. We need to find ways to verify that positive tests are true positives. The second problem is the lack of correlation to SARS-CoV-2 immunity (see below).

Near-term improvements: A number of new point of care immunoassays are under development that are likely to provide higher performance than the first wave of products. If successful, they will be well received. There is a focus on very high specificity.

The lack of correlation to actual SARS-CoV-2 immunity makes it difficult today to say what the meaning of a true positive serology assay is. Substantially more data is anticipated over the coming months. There are a number of labs investigating neutralization of SARS-CoV-2 or surrogate engineered viruses by patient- derived antibodies in *in vitro* cell culture (i.e., the virus is prevented from cell infection when the patient's antibodies bind to the virus). The relative potency of the antibodies in turn can be correlated to their titer and/or viral antigen epitope specificity. However, it is not known how the neutralizing viral test relates to actual immunity. The lack of reports of reinfection in convalescent patients is promising and research is ongoing. Recent reports from the USS Theodore Roosevelt indicate that only about 60% of those sailors that developed antibodies could neutralize the virus in neutralization tests. Lower ranges have also been reported.

Mid-term improvements: Although suggestions have been made to either retest positive samples or use more than one vendor's tests on each sample, without in-depth knowledge of the test design and performance with

interfering pathogens or substances, it is entirely possible that two tests would have the same sources of false positive results. In past epidemics, such as HIV in the 1980's, manufacturers developed reflex confirmation tests, such as western blots containing multiple separated proteins from the virus particle. These tests can be implemented in laboratory settings where samples from other labs are sent for confirmation. Confirmation tests are anticipated in the near future.

There are arrays of many SARS-CoV-2 peptides and peptoids (i.e., "proxy antigens") being tested with convalescent plasma that have been tested in neutralization assays. Recent data suggests that antibodies against spike protein might be more protective than those against nucleocapsid protein. The peptide or peptoid studies could take some time to complete but could lead to simple lab tests of an individual's level of protection.

As vaccines are developed it could be necessary to modify serology tests to differentiate vaccinated from recovered individuals. It is possible that antibody titer will be required in addition to antibody reactivity. Changes in antibody titer could be used to monitor changes in immunity in individuals or populations over time. This information could redefine the immune status of person and/or suggest that an immune booster is required.

SCREENING OF NON-SYMPTOMATIC INDIVIDUALS (ASYMPTOMATIC/PRE-SYMPTOMATIC)

The intended use: Although there are three intended uses listed in Table 1, this paper will focus upon one intended use; to determine if a non-symptomatic (asymptomatic or pre-symptomatic) individual has a current SARS-CoV-2 infection.

Populations to be tested: There are a number of subsets of the general population currently being screened or under consideration for screening tests. There is a great desire to continue to reopen local economies throughout the country. For this reason, the focus of this white paper will be upon employment-related screening of non-symptomatic employees. Many organizations are in the process of implementing testing of their employees in order to assess if they are able to once again join the workforce or remain within the workforce over time.

The testing protocols and timing are areas of active debate and trial. Currently, many healthcare professionals, such as physicians, nurses and other hospital staff, in close contact with infected individuals are tested regularly. In some locations, first line responders, such as firefighters and police, have implemented testing programs with a variable frequency of testing, from occasional (weekly or longer) to frequent (every one to three days), depending on the locale. Of particular concern is the level of risk individual employees might have of becoming infected and infecting others. The issues are complex due to variations in individual employee risk related to their living situation, social interactions, general health (e.g., pre-existing conditions), work environment and the general prevalence within the community in which the employee lives and works. See Table 2.

The living environment of an individual has a substantial impact on the risk of current infection. For instance, someone that lives in a free-standing home alone in a suburb is at a much lower risk of infection compared to a person living within a large family in a single dwelling, or a person living with family members in a condo where many non-family individuals are encountered daily, or a person living in a congregate living facility. The more an employee, while at home, is in continuous close proximity to multiple people free to move about outside the

home, the higher the risk of infection. However, when not at home or work, the individual will be at additional and variable risk due to their daily behavior ranging from walks near the home with proper masking and physical distancing to attending large gatherings in large urban areas. These are circumstances an employer is unlikely to be aware of and that can't easily be controlled.

Risk to individual employees and the rest of the workforce is dependent upon the work environment. In contrast to individual risk outside the workplace, this is an area often under the direct control of the employer. Employees who can work at home maintain their additional living, social, and personal health risks. Employees that work in environments where teams work together without physical interactions with non-employees during their shift (e.g., factories, offices) and where social-distancing precautions have been implemented are at substantially lower risk than situations where there is constant interaction with people from the local community (e.g., restaurants, retail outlets, street food vendors). At the far end of the risk spectrum are healthcare providers and first responders who must encounter persons known to be infected as part of their duties. PPE can be used much more effectively in some of these jobs (nurses, doctors) than others (firemen).

In overall low risk settings, it is entirely possible that the only time testing of employees would be conducted would be if they were symptomatic and the testing would be conducted away from the workplace. Then, they can be referred to their primary healthcare provider. They would re-enter the workplace after they recover.

There are attempts to assess employee risk of current infection prior to, or instead of, RNA testing. See health checks and surveys in Table 1. Some companies are using daily health surveys, often taken while at home, to determine if their employees can safely join the workforce. A tech company in Boise, Idaho, uses a series of questions about recent personnel interactions, such as visits with persons that recently arrived in the city by airplane. Other employers ask their employees if they have recently been contacted by a contact tracer or know that they have been in the presence of infected people. The CDC has listed a set of health-related questions to help assess risk of infection.

Beyond questions about potential recent exposure, the surveys can contain questions about health status such as fatigue, body aches, sense of smell (anosmia), and taste (ageusia). A number of reports suggest that the correlation of anosmia with SARS-CoV-2 infection is substantial and is often not reported by individuals without asking. It also appears that some people don't know that they have lost their sense of smell, prompting some groups to investigate "scratch and sniff" tests for detection of anosmia. The results of the surveys can result in a recommendation to self-isolate, seek care, return to work, and/or report for testing.

Others use, or are trying to create, health checks. Health checks may be useful in lieu of RNA tests or in addition to them. Temperature assessments and pulse oximetry are very common in Asia and Europe in office buildings, elevators, restaurants, airports, and many other sites of socials interactions. Many employers in the US have embraced this approach, for instance since April, CVS has been testing the temperature of its ~300,000 employees daily; anyone with a fever of 100 or greater is sent home. However, these methods can't be used to accurately assess current SARS-CoV-2 infection, particularly in non-symptomatic persons. Recent estimates suggest that 10-70% of the SARS-CoV-2 infections remain asymptomatic. Depending upon local prevalence and other risk factors, with these health checks alone there will still be occasional infections in the workforce.

The broad spectrum of conditions and risks suggests that one universal solution is unlikely. At this point, a global experiment is under way to determine how best to open the economy in a pandemic. As will be discussed, a systematic means to capture and trade experiences is sorely needed.

Use settings: Depending upon the population to be tested, the sites of collection and testing of samples will differ substantially. Some aspects of health checks and surveys could occur at the employee's home prior to going to work. Geisinger has announced a program to provide many of their members with thermometers and pulse oximeters at their homes. Home collection of samples such as mid-turbinate swabs or cup-collected saliva for shipment to a lab for testing has become more available over the last several weeks. However, there have been concerns expressed by some employers that suggest it would be better to have the sample collection observed due to the temptation for employees to provide samples from other persons to ensure that the employee remains employed.

Testing itself is being performed in a number of settings. It is common for samples to be sent to large labs off-site that can process the number of samples that are needed for frequent employee testing; however, it can take many days to receive results. Some lab services offer testing to employers. LabCorp introduced a return to work program in mid-May. However, recent discussions with Anthem Group suggest that more than a wait of one day for receipt of results would be very difficult for many of the employers that they serve.

Depending upon the size of the workforce, on-site employer testing can be conducted with dedicated staff and equipment. Most tests available are either moderate- or high-complexity, necessitating appropriate build out or availability of laboratory services. Some employers, such as Amazon, have decided to build dedicated labs to test their own workforce. Small systems that can process one test at a time are available, but with a test time of ~15 minutes for each sample run in series, it would take too long to process enough samples to justify such a system, except perhaps in a small workplace. Other point of care systems can process small groups of four to 10 samples in parallel. Workflows, costs, time to results, and frequency of testing will dictate whether or not on-site testing can be justified.

Another option includes mobile van testing. Point of care devices can be set up in a van and moved from site to site, which was done for Ebola testing in West Africa in 2014. Discussions with the company Amica in Canada that runs a series of assisted living facilities in a variety of locations indicated that they see mobile testing as a potentially cost-effective approach. This could be a reasonable alternative to the cost of developing an on-site testing option. However, there are associated regulatory issues as well as issues concerning sample collection, accessioning and tracking that must be considered for effective deployment.

At this time, antigen testing is under assessment as a reasonable alternative to RNA testing. If lateral flow devices or other simple formats can be introduced with adequate performance, it could be possible to test employees with finger prick blood or oral fluid samples without a laboratory. Many such tests have been introduced, but the evaluations are still under way by the Foundation for Innovative New Diagnostics (FIND) and others. Recently, there have appeared new FDA EUA claims for commercial antigen tests that limit the tested populations to the first five days after the appearance of symptoms when the viral load is usually quite high, and the antigen is usually detected.

General requirements of testing: The requirements for an RNA or antigen screening test are nearly identical to a diagnostic test with the following exceptions. As has been indicated, turnaround time is very important for many employers. If on-site testing is performed, and employees must wait for a result to begin work, longer than a 30 minute wait could be problematic. Some testing frequency models suggest that one- to three-day time to result could be effective in limiting most transmissions. In most situations, batch testing would be the preferred format to process enough samples. As a result, it is highly desirable to use collection methods that require less training and are less invasive than NP swabs, such as other nasal swabs or saliva cups or tubes. At this time, most of the testing will be in low prevalence settings.

False positive results will be an inconvenience to the employer (workplace productivity, need to locate temporary help, project delays, insurance costs) and to the employee (need to isolate, potential loss of wages, need to arrange for care for other family members during isolation, transportation costs, medical visit costs). Fortunately, the current RNA tests available rarely deliver false positive results. False negative results are far more concerning since a non-symptomatic but infected person could continue work in an environment where they could infect others. As a result, very high sensitivity is required. However, lower analytical sensitivity leading to false negative results could be offset by frequency of testing; that is, a person with a low viral load could test negative on test day one and is not infectious at that time, but when tested again one to three days later is at a higher viral load, is infectious, and is asked to self-isolate.

Status of testing, unmet needs: Some existing RNA tests do suffer from false negative results for at least three reasons. Some tests were developed early in the pandemic and design of the primers/probes does not permit adequate binding to the viral RNA. Due to the testing technology employed, some tests' lower limits of detection are probably too high to pick up early or late infections. Sample collection is not always performed properly. Next generation versions of tests are in development to deal with some of the shortcomings. It is important that purchasers carefully consider the features of the options available. The frequency of testing required will increase the cost consciousness of employers. The typical diagnostic tests often cost over $100. This price could increase further with deployment of differential diagnostics, for example during the upcoming flu season. As the burden of cost moves further toward the employers themselves, lower cost tests will help drive adoption.

Near-term improvements: Home or simple on-site collection of samples will help increase testing substantially. The trend to switch away from NP swabs is essential. The FDA has changed the wording in their guidance document to manufacturers to include other sample types. Point of care RNA systems should become broadly accepted in moderate complexity on-site labs or in mobile labs. On-line algorithms using health surveys and checks for selecting who should be tested will help select who should be screened with RNA tests. Those that test positive will be connected to contact tracers and asked to self-isolate. More and improved antigen tests will appear in lateral flow and other formats, but the minimum level of acceptable performance, particularly false negative results, needs to be refined. Pooling algorithms are likely to be implemented.

A number of organizations have developed next generation sequencing methods (NGS) for SARS-CoV-2 RNA. Recent reports from the University of California San Francisco (UCSF) indicate that there can be detectable changes in the viral sequence in as few as two transmissions. As a result, it is possible to track the viral variants across time, populations, and locations. Epidemiological NGS studies within hospitals have been conducted that

show the probable sources of initial infection and the likely mechanism of spread. It is likely that some employers will embrace this technology to monitor their workforce.

One of the use cases identified in Table 1 involves environmental testing. It is possible for employers to obtain testing of their facilities and validation of cleaning practices with RNA testing using surface swipes and other forms of sample collection. This type of testing is common in the food manufacturing industry. Environmental testing could potentially help to identify sources of transmission. It could also increase the confidence of the management and staff if practices to decontaminate the work environment are demonstrated to be effective. There are potential complications in environmental testing due to the possible detection of non-infectious RNA contaminants that will not lead to transmission. These challenges will need to be resolved.

Mid-term improvements: It is probable that health survey questionnaires can be formally tested for sensitivity and specificity as a form of triage testing for use in conjunction with an RNA or antigen confirmation test. This could dramatically improve the cost effectiveness of the overall testing process. Better, simple health checks such as anosmia tests could supplement surveys for better risk assessment. The use of questionnaires and simple measures of health status should become integrated with RNA/antigen screening testing. If efficacious and affordable antiviral drug therapy is developed and successfully deployed, the entire process to screen employees could change. Perhaps there will be no continued need to track non-symptomatic employees since once symptoms appear, they will be referred to their respective healthcare systems to obtain medication.

CONCLUSIONS AND NEXT STEPS

This white paper is a portion of a larger project involving the Rockefeller Foundation, Arizona State University and Duke University to develop SARS-CoV-2 testing protocols for employment, school and community settings. The description and assessment of use cases for testing populations in these settings is fundamental to achieve this goal. Three use cases were prioritized for the analysis in this paper: diagnosis of symptomatic persons, previous exposure to SARS-CoV-2, and screening of non-symptomatic persons.

Diagnosis is mostly conducted by SARS-CoV-2 RNA testing. There are many tests available and more are coming. Challenges include sample collection, test design and limits of detection, resulting in some cases of false negative results. Laboratories find it challenging to maintain the supply of tests from manufactures, and as the number of tests per day required continues to increase, the challenges will continue to mount. One solution that is being broadly investigated involves pooling of four or more samples, although there are concerns about poorer limits of detection due to the dilution factor. Another potential improvement is to qualify persons selected for testing more effectively based upon risk assessment (e.g., triage) with the intent of testing fewer total people to identify an equal or larger number of infections. The test-positive rate in most US locations is less than 10%. Antigen tests have appeared and could help to decentralize testing to smaller clinics or home testing, if the performance is adequate.

Tests of previous exposure are conducted with antibody tests. There is a great desire to correlate these tests with immunity to reinfection. So far, none of the commercially available tests can provide this assurance, though research is currently ongoing. A great deal of effort is being applied to the development of new tests that have been designed to detect the subset of antibodies that are capable of neutralizing SARS-CoV-2 infection of cells in

culture assays. Unfortunately, at this time there is little use for these tests in the reopening of society. Although not expanded in this paper from Table 1, population surveillance with serology tests does, and should continue to, add value in the assessment of the current status of and future changes in SARS-CoV-2 infection prevalence as improvements in treatment and control of transmission are introduced.

Screening of non-symptomatic persons is under consideration in the three use settings of interest for the project. Significant challenges exist to implement testing protocols that could be useful. In this paper, the focus is on employer settings. Of great concern is whether or not employees can reenter the workforce without becoming infected by other employees or transmitting infections to others. Testing all employees on a regular schedule has been implemented by some companies, while others struggle to know what to do. The RNA tests used for diagnosis are the main candidates for screening tests. However, there is a greater emphasis on time to result so that employees can safely enter work without waiting hours or days. Many employers are using health surveys and health checks, often every day, to locate persons who should be isolated. These methods need to be systematically coupled to testing protocols.

Using the use cases and settings, the project team is proceeding with testing protocol development for the three selected settings. The process includes determining who should be tested, description of the sites of sample collection and testing, workflow analysis, and test performance requirements. Target product profiles will be developed to describe tests that will be required including specifications for ease-of-use, sensitivity, specificity, time to results, level of training required, costs, process to deliver results, and other factors critical to successful testing. Testing frequency will be based upon the level of infection risk in the settings (likelihood of infection, risk of transmission, and the effects of transmission). The progress of the project team will be reported on an ongoing basis.

The COVID-19 pandemic has led to probably the largest scientific investigation of a disease in all of human history. At its best, science is a self-correcting body of knowledge. The pace at which the COVID-19 knowledge base grows and improves means that reviews such as this white paper will require correction over time, perhaps within days of its release. Please bear with us.

Living Conditions	Social Interactions	Workplace
At suburb home alone	Sheltered in place at home	Work from home
At suburb home with family	Physical distancing and masks for outings: occasional grocery shopping, hardware store	Small self-contained employment site, no interaction with public: small factory, office
In urban apartment building	Occasional physical distancing and masks in partially open city: city walks, parks, jogging	Large employee site with many internal interactions, no interaction with public: large factory, company headquarters
In congregate living facility	Social distancing and masks in small groups: church, restaurants	Employees have occasional interactions with public: law firm, accountants
Any of the above with preexisting conditions	Close interactions with service personnel where protection is difficult: hairdressers, dentist office	Employees have constant interactions with public: grocery store, clergy
Any of the above in a high prevalence setting	Large gatherings without protection: sporting events, crowded bars, concerts	Employees work persons with known COVID-19 cases: nurses, doctors, first responders

Table 2: Three categories of SARS-CoV-2 infection risk to employees, listed from low to high. The risk is ranked within each column and not across columns.

1) Larson, E. & Larson, R. (2004). Use cases: what every project manager should know. Paper presented at PMI® Global Congress 2004—North America, Anaheim, CA. Newtown Square, PA: Project Management Institute.

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