Diagnostic Playbook

Focus on COVID-19 Use Cases

DEC 6, 2020

ENGAGEMENT GROUP
HORIZONS, DIAGNOSTIC PILLAR
MGB CENTER FOR COVID INNOVATION

Contents

Introduction

Beginning in March 2020, the Mass General Brigham Center for COVID Innovation Diagnostic Pillar brought together over 400 diagnostic experts from around the world to gather information on testing for SARS-CoV-2 and COVID. The task was simultaneously straightforward and complex. Straightforward in the sense of a search for quality, clinical utility and availability. There was a flood of devices from proven and unproven diagnostic manufacturers, a moving regulatory framework, insufficient supply chains and potentially spurious claims of quality.

An important aspect of the work of the Diagnostic Pillar Working Groups was the collection of survey data and qualitative interviews on test requirements and use cases during the pandemic. Clinical laboratorians, healthcare workers, investors, transportation leaders, public health officials and others were contacted. It is with deep gratitude that, during a pandemic, many were kind enough to take the time to share their thoughts on a range of topics. What is the needed test result turnaround time (hoped for, acceptable, not useful)? What is the clinical utility of a test result over a variety of test types (PCR vs Antigen vs Serology)? How do particular test categories meet the return to work, contact tracing and pandemic suppression needs? What are the supply chain concerns in a given use case such as a school, an airport, a business, a hospital?

In addition, to help guide early inventors of early stage diagnostic tech, we created a playbook with an overview of the licensing process and startup formation. This guide contains information aggregated from the tech transfer offices, investors, companies, entrepreneurs, and end user experts. We hope that this can serve to as a starting point for commercialization of new technologies.

It has been less than a year of painful global pandemic experience building. As of this writing, over 40 million people have been infected globally and over a million have died. In the diagnostics arena, a previously standard and answerable question as to what sensitivity and specificity must be required of a test has changed multiple times. As the pandemic progressed, needs changed, crises bloomed and clinical use cases appeared and were overwhelmed. What was thought to be required in terms of sensitivity and specificity changed to what was acceptable under certain situations. The answers to the following survey questions must be considered in the context of being given during a crisis, with incomplete information and an uncertain future.

The information gathered here provides a view of how diagnostics can be developed in a crisis and how those tests are considered by a wide range of individuals with different pandemic response responsibilities. The information also teaches us that, when responding to a novel threat, it is best to listen to a number of voices speaking from different vantage points in order to best meet the demands of a global population at risk.

Current Opportunities and Challenges in COVID-19 Diagnostics

PHYSICIAN SURVEY RESULTS

We conducted a survey in July, August 2020 and received 39 responses from clinicians and public health professionals. RNA is the expressed gold standard analyte type for COVID-19 diagnostic tests; opinions vary as to using PCR alone or together with antigen and/or serology testing. There was a clear call for decreased time to answer, improved test performance, broader test access and improvement to supply chain issues. The majority of

respondents were interested in rapid tests (less than 2 hours). Physicians preferred anterior nasal and saliva samples. Full results from the survey are displayed on the MGB website (https://covidinnovation.partners.org/).

Some of the key challenges mentioned by physicians were around the differnetial diagnosis of COVID-19 vs. other diseases.

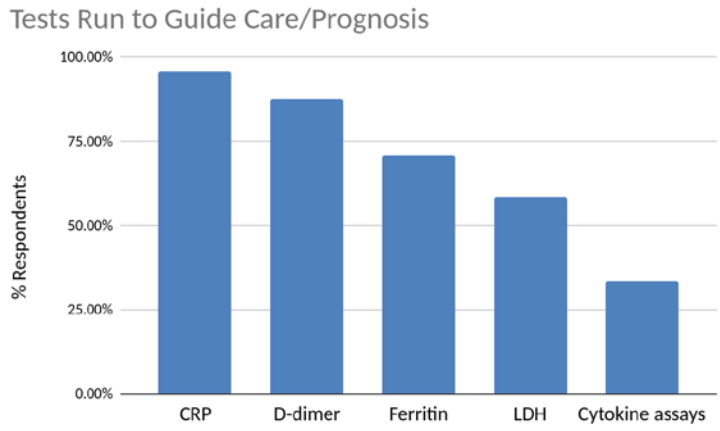
> *"Diagnosis is difficult, since in kids a lot of this could also be strep, I often end up empirically treating for strep, since we're not allowed to do strep swabs (aerosolizing procedure)."*

> *"Chest x-ray and other chest imaging as indicated (chest CT, lung ultrasound). If COVID is suspect and confirmed, we usually order basic labs (CBC, CMP), procalcitonin and blood/sputum/urine cultures as indicated to rule out co-infection, and tests for atypical pneumonia (urine legionella/strep/mycoplasma IgM/IgG) if COVID is negative. Inflammatory markers. Depending on severity of illness if COVID is suspected but the COVID PCR is negative, we may send a respiratory viral panel to rule out other etiologies of viral pneumonia."*

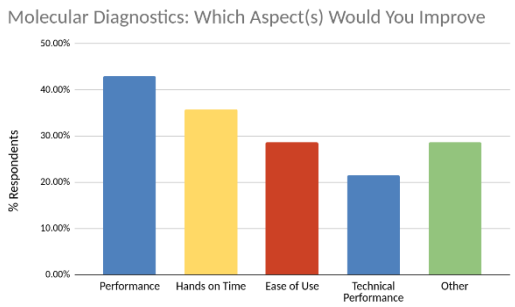
> *"I ask every patient if they have fever, cough, shortness of breath, itchy eyes, loss of smell, sore throat, or purple toes. I also look at their results of the nasopharyngeal swab and CBC with differential (most surgical patients have one). I asked them about recent travel and known contacts."*

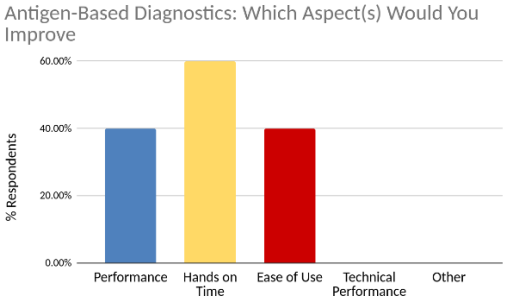
> *"We query: anosmia, fever, shortness of breath, hypoxemia, rashes, diarrhea, URI, and cough."*

Physicians also mentioned that they were running several other tests in addition to COVID-19 tests.

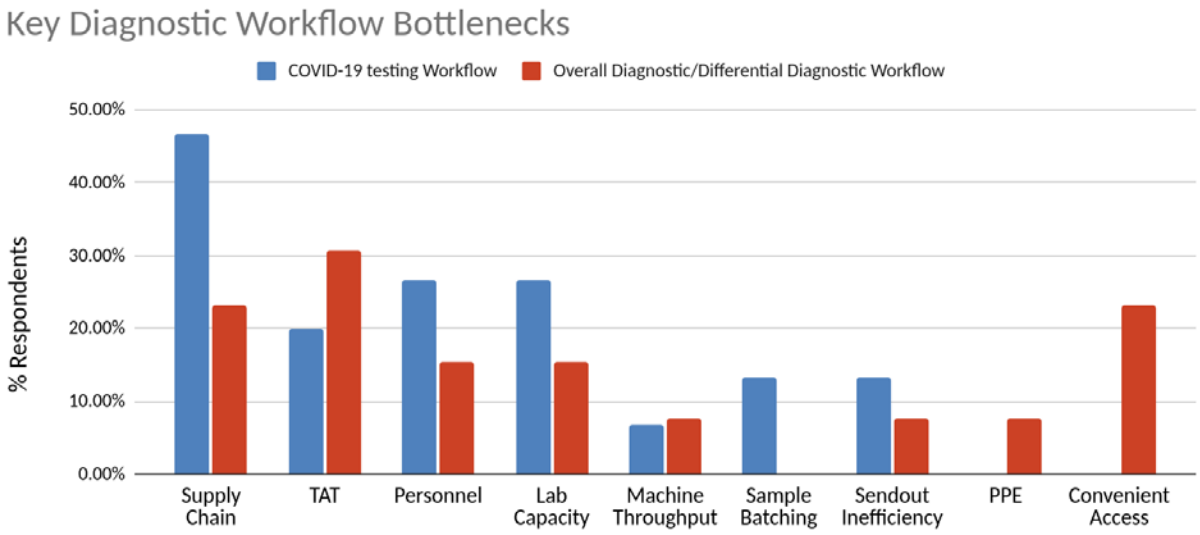


In terms of improving, SARS-Cov-2 molecular tests, the main areas that physicians wanted to see improved were overall performance and hands on time. For antigen tests, physicians wanted to have better performance, hands on time, and ease of use.

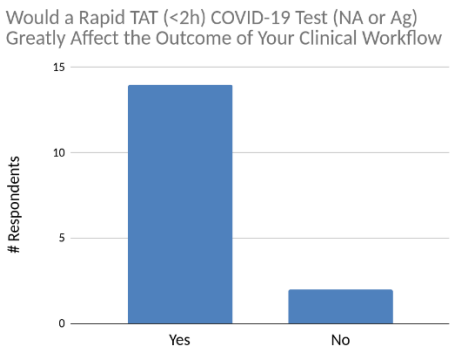


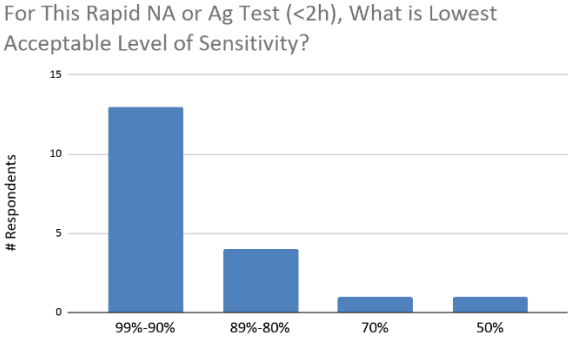


For bottlenecks in the work flow, supply chain was cited as a major barrier of COVID-19 testing.

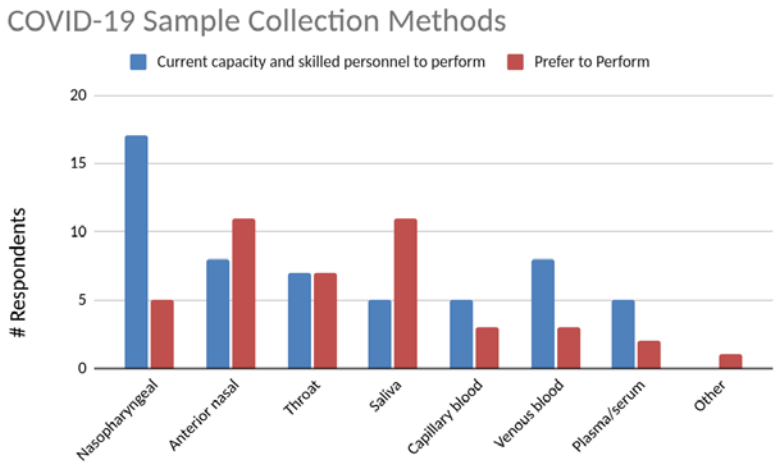


Physicians are very interested in rapid testing, and the majority reported that a rapid test with “time to answer” of less than 2 hours was desired. The expectations for performance of a rapid test are high with most reporting a sensitivity requirement of 90%+.

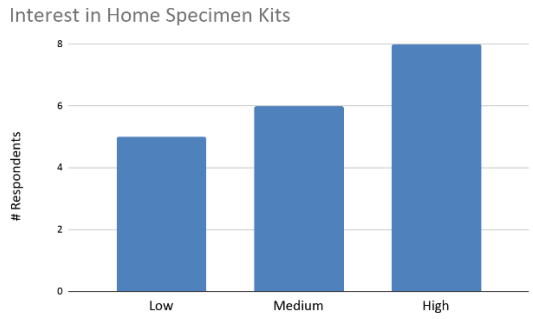


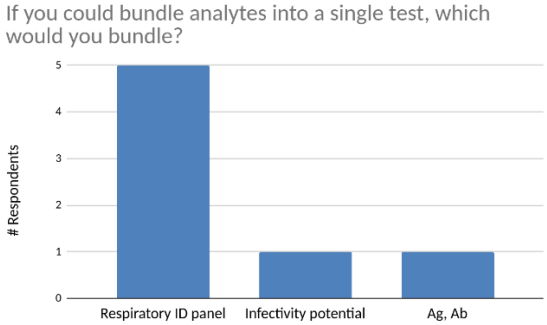


Physicians were most likely to be performing nasopharyngeal sample collection, but prefer other sample collection methods.



Most physician were “highly” interested in home specimen collection kits. The majority of respondents would also like to bundle a respiratory panel, from the options provided.





As a part of the survey, physicians could provide open responses to questions and described their needs in more detail. In the table below, please find key comments, grouped by theme.

Category, (Frequency)	Comments/Calls
Patient/Practice Safety; PPE (4)	"Difficulty keeping staff safe from patients refusing to wear masks or coughing when they do a nasal swab"; "Need safe way to evaluate the patients in outpatient settings"
Specimen Type (3)	"Need saliva or rapid fingerprick blood testing"; "A sample type that is not the nasopharyngeal"
Venue (3)	"Rapid testing that is accurate and done at home"; "Rapid POC 15-30' test with low false negative rate"
Understanding COVID-19 Disease Manifestation (2)	"Understanding Covid and what symptoms to expect, length of time for being sick"; "It can be very mild to very severe, must always be considered, which at times can make other diagnoses hard to consider or focus on"
Reimbursement/Free Testing (2)	"COVID-19 testing should be free for all at all locations"; "Must address reimbursement, administration support, complete indifference"
Contact /Asymp Testing (2)	"Testing contacts of all patients who test POS"; "Tests for asymptomatic pts with contacts to COVID"
Test Admin Time-Consuming (1)	"The lab TAT is long; acquisition is time consuming for staff"
Electronic Medical Report (1)	"Better EMR reporting of date of symptom onset (DoSo), in terms of both accuracy of reporting/recording and finding it in the EMR would be helpful. DoSO matters a lot for interpretation of test result/sensitivity"
Symptoms/Progression (6)	"ARDs biomarker; Predictor of hypoxemia"; "Pulmonary or lung reserve to handle the infection; sum the size of the infiltrates seen on the radiology"; "Predictive test of who is going to progress to cytokine storm"; "Understanding the viral load associated with symptomatology. Which risk factors make infection more likely despite negative PCR (with low sensitivity)"; "COVID prognostic bundle with CRP, ESR, ferritin, LDH, absolute leukocyte count and Troponin"; "a biomarker that can accurately predict a patient that has a high likelihood of decompensation requiring hospital admission"; "Predictor of outcomes"
Risk (2)	"Current approach: treat everyone the same. Need data of who might be at risk for infection and if infected, who would be at risk for worse outcomes (need for hospitalization), and if hospitalized, specific therapeutic approaches to reduce the CV and pulmonary complications."; "Risk factors; biomarkers for chronic diseases"
Tests: Access, Performance, Supply, TAT (7)	"Access to testing, accuracy of testing"; "Speed of testing /results"; "TAT"; "Getting enough testing done (3)"; "Rapid diagnostics of multiple pathogens "
Differential Diagnoses (6)	"Separating COVID from other respiratory viral illnesses (4)"; "Antibody testing with poor specificity given prevalence giving more false positive tests than true positives "; "Distinguishing the primary driver(s) of symptoms";
Screening (4)	"Prevention and screening"; "Population screening"; "The amount of asymptomatic patients "; "100% sensitivity/specificity for detecting live virus in all people"
Treatment/Prevention (5)	"Early treatment to attenuate the disease to prevent respiratory failure and long term sequelae of lung disease" (2); "Oral vaccine that is effective with low SE profile and long protective period (3)"
Diagnosis/Differential Diagnoses (3)	"One swab, any type that would run a full viral panel on one sample with a turnaround time <1 hour with good sensitivity and specificity"; "Ct values accessible to ID physicians in EPIC, consideration of sputum induction for COVID-19 diagnosis via LRT specimens in select cases"; "A point of care test that is both sensitive and specific. Also a test that gives a viral load so we know patients that likely are going to "tank" over the next few days and we should hospitalize to maximize therapy"
Epidemiology/Research (3)	"Note success with contact tracing in Canada/elsewhere. Local outbreaks reported daily in newspapers"; "Co-purification of RNA and DNA from swab samples to sequence metagenomes and host DNA"; "Kits that could be mailed to patients with results reported remotely to a central database and compiled to determine demographic and geographic information for potential hot spots"

Access, Protocol (2)	"Test every patient admitted to hospital or had a perform procedure"; "Testing available on every corner for free in an urban area"
Miscellaneous (9)	"Great to have Ct values from SARS-CoV-2 NATs more accessible in the EMR"; "Biomarkers--Ab levels to different antigens in the COVID virus"; "Age, race"; "The death rates per capita and the R-naught and related measures should be available most readily and locally." "Lack of availability of testing to low income patients"; "Finding safe locations for rapid testing"; "Contact tracing is essential to reduce the virus. Get volunteers to help reduce costs"; "How to interpret persistent positive tests (i.e. prolonged shedding >90 days), how to interpret positive molecular test in the setting of remote antibody positivity (re-infection?)"; "Accepting the new normal"

QUALITATIVE INTERVIEWS OF KEY STAKEHOLDERS

The coronavirus pandemic is reshaping the economy and the healthcare system in many different ways, some of which will open up new opportunities for commercializing technology that were not previously available. In addition to the survey data summarized earlier, we completed long-form interviews of experts in investment, industry, medicine and public health to better understand the emerging opportunities for new tests. Our findings indicate that the initial set of needs for diagnostic testing for the pandemic are slowly being addressed by a mix of existing diagnostic players and new entrants who were available to secure new investment or additional investment into their platforms in 2020. For those who are focused on COVID-19, speed and execution are critical. However, despite the scale-up of currently available tech and new emerging tech, there will continue to be new opportunities emerging. Below are some of the trends that are expected to impact new innovation in diagnostics:

Investment in Healthcare

In the first half of 2020, diagnostic investment was up a considerable amount. SVB reported that COVID-related companies raised $1.3B over the first half of 2020. Many investment groups have already placed their bets on emerging tech for the pandemic; however, there are still opportunities for innovation for tech platforms that can address a variety of needs related to other trends. In addition, economic uncertainty makes healthcare investments a safer bet than other sectors.

Continued emphasis on digital health and the shift to telemedicine

Many primary care providers and other outpatient providers rapidly shifted to telemedicine in March 2020. At first, providers reported that the shift was chaotic with multiple systems for communication with patients being used at individual practices, and some patients having trouble connecting to those systems. However, those practices report that they have settled on specific tools for communication and better IT support for their patients.

The one gap with the shift to telemedicine is laboratory diagnostic testing, which when ordered requires patients to travel to a laboratory site for a blood draw. There will be new opportunities for expanded opportunities for patients to either ship capillary blood samples to labs for testing or have remote home-based testing because of the new telemedicine capabilities of many providers. It is likely that a large portion of these visits will remain remote, even after the pandemic, given the cost savings and convenience. The promise of telemedicine is to bring healthcare to the individual, not the reverse. The diagnostics challenge with telemedicine is that the patient is not in the doctor's office for venous blood draws for laboratory testing. If the doctor orders a test, the patient must make a trip to a lab for the blood draw. Given the shift to telemedicine, there will likely be new opportunities for more convenient diagnostic testing. In some cases, nurses can be deployed to a patient's home to collect a sample. However, this still

creates a point of contact for possible virus transmission and may not be feasible in all locations. In response, companies are creating a mail order testing market for blood samples (e.g., Let's Get Checked and EverlyWell). The healthcare provider or patient will order a test, a sample collection kit will be sent in the mail, the patient will provide the sample using the kit and then ship the kit to the lab for analysis.

This shift to telemedicine will likely create more opportunities for home and mail-based testing. In addition, non-invasive tests with smartphone tech could be increasingly helpful to measure a variety of conditions. The keys to success for this type of testing will be defining the essential biomarkers for tests that are currently not easily available at home and have a clear clinical utility, integrating into the telemedicine workflow, working closely with regulators, defining the sample type for testing (e.g., capillary blood, saliva, urine, stool, hair), and defining pricing and payment/reimbursement strategies. Turnaround times will also be important, as timely information will be critical to providing and guiding treatments, especially for certain therapeutic areas

As part of this telemedicine shift, there may be more opportunities for home-based healthcare for the elderly due to the disruption of many nursing homes caused by the pandemic. For safety reasons, an increasing number of families are choosing to keep elderly relatives at home with help from health aides. This shift to home-based care will open up new opportunities for diagnostics.

Distributed testing; Interest in making community spaces safe

Reopening schools, hospitals, airports, and other public spaces will likely require a combination of public health measures and testing protocols until a consensus is reached regarding public safety in a post-vaccine environment. Given this shift, there will be new opportunities for diagnostics to integrate with these systems with innovative tech and payment models. In addition, there are opportunities for rapid, low cost pooled testing and screening tests with slightly lower sensitivity to help meet these needs. There may also be new opportunities for environmental testing of surfaces, wastewater, etc. to help monitor outbreaks.

Airports and airlines:

Airports are a particularly challenging environment for infection control. At major airports in the US, thousands of workers and over 100K passengers may pass through the terminals each day in non-pandemic times. People may be traveling domestically or internationally, sometimes with multiple stops. COVID-19 testing protocols and infection rates can vary dramatically by location. In addition, passengers will be in close quarters at security checkpoints, waiting areas, and on airplanes. Airports also have quarantine procedures for flights, if a passenger is suspected to be ill.

In the US, some airports are being testing procedures. For example, JFK, Newark, and LaGuardia airports have COVID-19 testing sites. JFK terminal 4 originally offered tests to airport and airline workers in June 2020, but then expanded testing for travelers. At JFK terminal 4, the Abbott ID Now system is used for rapid testing, and the instruments were located in a space previously used for a spa. As of August 2020, the XpressSpa was in discussions to expand testing to up to 60 airports in the US. Testing at US airports was not mandatory, but was offered free of charge in summer 2020. Passengers from affected areas who travel to NYC are currently required to fill out a form and quarantine for 14 days. Other countries (e.g., UK and Germany) require that passengers either show proof of a negative test within

48 hours or receive a test at the airport and quarantine until the results arrive. In addition, airlines have partnered with testing companies for travel to certain locations. For example, American Airline partnered with LetsGetChecked for mail-based testing and CareNow urgent care at Dallas Fort Worth international airport for onsite testing. In order for a new tech to be adopted at an airport, it would need to be (1) significantly faster and/or easier to use than existing tech, (2) only an incremental charge relative to an airline ticket, (3) catch most positives.

Challenges for adoption at airports will depend on the local regulations and airport management (e.g., is the airport private or municipal). In addition, new companies would need to work closely with airports to identify testing spaces, likely outside of security for travelers entering the airport, and a testing space for travelers arriving via airplanes. Protocols will need to be developed for communicating results to passengers, quarantine space while waiting for results, what passengers need to do if positive or negative, communication with airlines, etc…. In addition, the test could be self-pay or a fee on a ticket, if there is coordination with airlines. Despite the challenges, there is a willingness at airports to help control the spread and increase safe air travel.

Hospitals:

Hospitals are another challenging environment for COVID-19 control. Patients with serious, symptomatic respiratory illness are presenting to emergency departments, and the clinical staff needs to make decisions on if they should admit a patient to a COVID ward, other ward, or treat and return home. Hospitals have a variety of ways to handle this situation. Some are testing patients for coronavirus before entering the hospital, if they have access to rapid testing (1-2 hour turnaround is typical, including workflow). Others are testing patients in a central lab, and may have to wait hours for results. At this setting, screening tests and very rapid, low cost tests could help triage patients.

Many hospitals are requiring coronavirus testing prior to receiving an elective procedure (there is also testing before emergency procedures to help with safety protocols). For elective procedures, a longer turnaround time for test results can be acceptable. For example, the patient could come to the hospital or other clinical for the coronavirus test 24 hours before their procedure. However, in a subset of cases this can be logistically difficult. For example, if a patient must drive for hours in order to reach a hospital, a rapid test the day of the visit is preferred. Rapid tests are also more convenient for all patients. In order for a new technology to be accepted into a hospital setting, it would need to be significantly superior to the market leaders in rapid PoC testing or if no test exists, then the new tech would have to meet the key requirements of the users.

Independent community hospitals in the 100-200 bed range have most of the same challenges described but do not have the resources, connections or leverage that large hospitals or hospital systems are using in response to the pandemic. These smaller hospitals often find themselves competing in an environment dominated by larger entities able to negotiate volume based supply agreements, stockpile significant volumes of needed items and complete in house validations of new diagnostics. Providing proven solutions to diagnostic needs suitable for lower testing volume environments can, in the aggregrate, be a significant growth opportunity for a smaller vendor. In the absence of such solutions, smaller hospitals are left making difficult choices between appropriate healthcare, diagnostic testing use, PPE availability and caregiver safety.

Schools and Universities:

The situation with some schools reopening, while others remaining remote is very fluid. Repeat testing of students and staff could help control outbreaks in schools that have resumed in-person and on campus learning. Some schools are trying out innovative testing programs. For example. Purdue University partnered with Vault Health, a saliva-based mail order test for COVID-19, and students who are returning for on-campus learning are required to take the test 48-72 hours before their planned arrival on campus. UC San Diego launched a "return to learn" program, which involved students self-administering a nasal swab and then dropping the swab off at sites around campus for testing. Some schools are also offering testing before students return home for holiday break, and a few are requiring testing compliance in order to have a return to campus (e.g., Notre Dame). Some large school systems are also affiliated with hospitals and using those facilities for on campus testing.

Some public school systems have partnered with local organizations to have broader surveillance testing to help monitor outbreaks. For example, the cities of Medford and Somerville Massachusetts partnered with Tufts University to provide low cost testing to faculty, staff, and students for the K-12 schools. However, many school systems are relying on community resources and testing facilities to help control outbreaks.

Interest in preventing the next pandemic

The current situation is making people in every industry think about preparedness for the next pandemic. This new thinking will open up opportunities for tech that can help everyone be prepared, especially company leaders who are now expected to make an increasing number of health decisions for their employees. Although it is unlikely (but possible) that another pandemic of respiratory human disease will occur in the next few years, many industries may now think differently about infectious disease and their employees. In addition, after the current pandemic, there will likely be continued interest in animal epidemics that impact food security and pharmaceutical products. For example, Sub-Saharan Africa, Eastern Europe, China and southeastern Asia are battling a major outbreak of African Swine Fever (ASF). The current prevention methods involve culling entire herds to stop the spread. Such culling (now well into the millions of animals) has resulted in global shortages of heparin as the API is predominantly made from porcine intestinal mucosa. Low cost, animal diagnostics for monitoring health and outbreaks could help alleviate this situation.

Supply chain innovation

The inter-connectedness of the world was revealed with the pandemic. Given shortages of several materials because of oversees suppliers, there are opportunities for new tech that is either (1) simpler with fewer components and/or (b) has components that can be locally sourced.

Understanding the efficacy of emerging vaccines and immunity for individuals who have been infected.

The most commonly run tests for antibodies do not test for neutralization, and testing T-cell response is not commonly completed at a population scale. There will be continued needs for understanding "true" immunity to coronavirus and also understanding antigenic shift of the virus over time.

As a number of vaccines are expected to be approved in the coming years, understanding the immune response and protection conferred by a vaccination may be needed. For example, if the vaccine only has partial efficacy, it may be necessary to test those who are vaccinated to determine the need for boosters. The market is currently viewed as being saturated with antibody tests, but there may be opportunities for tests to measure other types of immune responses. There may scenarios that develop where testing both the antibody and cellular response is of clinical, and thus commercial, value. This is very speculative and depends on the type of vaccine approval scenarios that will arise in the coming years. Also, tests that can distinguish infection-induced from vaccine-induced immunity will be important.

Novel testing modalities

Simpler non-invasive testing modalities will help with population screening, diagnosis, and monitoring. For example, emerging technologies are focusing on testing breath, heart rate, and/or pulse/ox to screen for those at who may be infected and to monitor the need for hospitalization in infected individuals. These methods could have continued use in monitoring for other infectious diseases.

Respiratory Panels

There are opportunities for rapid testing for respiratory panels. As of this writing, the fastest test identified by our team is the BioFire assay with 1 hour turnaround. Hospital physicians reported that this test was very helpful with triage for patients who present with respiratory illness to the emergency department. In order for a respiratory panel to be adopted, it would need to expand the test menu, be significantly faster (E.g., minutes), or be incredibly easy to administer (staff with minimal training could run it).

Startup Considerations

We also asked experts in company formation about key considerations for startup companies in this space. We summarized the considerations in the table below. Many emphasized the importance for a tech to be relevant beyond COVID-19, even if the commercial plan involved a COVID-19 test as the first product. The window for rapid authorization and commercialization may close in 2021 for the nucleic acid and antigen tests, depending on the public health situation and utility of already available tech.

Question	Startup Importance	Additional Info for Diagnostic Technology
Unmet need or problem being addressed?	Answers the "Why do this at all?" question	What is the potential clinical utility of this invention? (How does it impact/improve clinical care or decision-making or public health?)
Who has this need/problem?	Addressable market data	What setting will this be used in? (central lab, point-of-care, or other [e.g., home]) How does it fit into the current workflow? [need full work flow mapped out from sample to answer] Who will be ordering or purchasing the test? (e.g., consumer, physician, other healthcare worker)
Who currently delivers this solution?	Addressable market data Market research reports	Is this a new area? (e.g., home diagnostics) Are there existing competitors?
At what stage is the solution? Concept? Early prototype? Proof of Concept Data? Validation Data?	Provides investors with the level of risk to investment and the timeframe involved	Level of data required for investment discussed in the "startups" section of the companion translational document.
How similar is the approach to existing products?	Competitive advantage	Look at competition two ways; by clinical indication and by tech platforms
Does the approach answer a single need or is it a platform to answer other needs?	The difference between a single product and a future product line supporting an entire company	Does it require the use of new or existing equipment? How widely distributed/used is this equipment? Are there multiple manufacturers or just one?
Who competes in this market?	Risk to success in competition with a better funded competitor. If no competition, risk to build that market from scratch.	For startup, diagnostic invention typically needs to be 100x-1,000x better on one factor or 10x-100x better on two factors (e.g., sensitivity and time to results), compared to competitors. OR completely new market/capability. In addition, needs clear use case and easy workflow.
How big is the market?	Detailed data needed on addressable market (all potential users), target market (subset of likely users at start), adoption ramp (related data on likelihood of changing current practice)	Diagnostic specific market research reports and annual reports from public diagnostic companies can be helpful (E.g., Quidel)
Pricing/Reimbursement	Cost of goods, cost to manufacture, acceptable margin by market, reimbursement environment for solution	For diagnostics, remember to think about pricing along the supply chain. For example, a newco may sell a test to a distributor at $1. The distributor might sell that test to hospitals for $10. The hospital might be reimbursed at $20. Also need to consider the current reimbursement for competing solutions. An older solution, with better reimbursement, would outweigh a new, or better, technical solution CMS fee schedules at https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files

Regulatory requirements	Level of regulatory rigor needed concerns needed funding and timeline.	US Diagnostic regulatory approval categories (see startup section for more details) EUA LDT / CLIA 510(k) PMA
Management	Are the academic inventors leaving to form the company? If yes, what makes you think they will succeed? If no, do they have an experienced entrepreneur to take this on?	What experience does the team have with diagnostic commercialization, regulation, and reimbursement?
Budget	What is the investment needed to further develop? What does an exit look like?	For startups, think about investment needed to get to next value inflection point (more details in the startup section)
Intellectual Property Strategy	What type of IP do you need for a startup? How will you protect the newco from competitors?	Is the technology critically reliant on any IP that is not controlled by the NewCo or licensee?
Licensing strategy	Exclusive is most likely. If not, need a clear rationale to start a new company without that competitive advantage.	For startups, think about if additional licensing deals are needed with your suppliers/partners

APPENDIX

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APPROACH TO RESEARCH

We consulted the expertise within the MGB COVID Innovation Center and interviewed additional experts to supplement our research. *External Primary Research:* Interviews were conducted summer/fall 2020 with the following groups of people: Investors (n=5), entrepreneurs (n=2), Airport executive (n=1), company executive (n=1), US physicians (n=3). In addition, we consulted trade articles, industry reports, scientific publications, and entrepreneurship books. Key references are highlighted below.

Special Thanks to Guidepoint https://www.guidepoint.com/ and GLG https://glg.it/ for donating their services to connect us with experts.

KEY SOURCES

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