Horizon Technologies

Diagnostics Opportunities Assessment
Summer 2020
Diagnostics Opportunities Assessment

**Mission: Drive the Innovation and Development of COVID-19 Testing**

Beginning in March 2020, the Mass General Brigham Center for COVID Innovation Diagnostic Pillar brought together >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;
- Complex in terms of the flood of devices from proven and unproven diagnostic manufacturers, a moving regulatory framework, insufficient supply chains and potentially spurious claims of quality.
It has been a year of painful global pandemic experience building. As of this writing: >40M people infected globally, >1.1M have died.

- In the diagnostics world, previously standard/answerable questions such as: 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, were addressed, only to have others arise.

- Requirements for sensitivity and specificity, and other performance metrics, changed and adapted to multiple situations and evolving use cases.
Goal: To ascertain current COVID-19 clinical diagnostics unmet needs, bottlenecks, future opportunities

An important aspect of the work of the Diagnostic Pillar Working Groups was the collection of survey data on test requirements and use cases.

Physicians, clinical laboratorians, healthcare workers, public health officials, and others were contacted. Despite being in the midst of a pandemic, many took 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 over a variety of test types (PCR vs Antigen vs Serology)?
- How is test performance in a variety of use cases?
- How well do test categories meet clinical needs (COVID Dx and Clinical practice screening), and pandemic suppression needs?
- What are the supply chain or test availability concerns in a given use case?
- What challenges remain?
Goal: To ascertain current COVID-19 clinical diagnostics unmet needs, bottlenecks, future opportunities

Detailed survey sent out July, August 2020
- Survey Monkey
- Closed, Multiple choice, Open Response, Comment formats
- Skip Option

Recipients
- Mass General: Brigham Network
- Guidepoint, Inc Market Research Network

Responses (39)
- Primarily physicians
- Distributed across diagnosing and screening use cases
Goal: To ascertain current COVID-19 clinical diagnostics unmet needs, bottlenecks, future opportunities

- Survey answers should be considered in the context of being given during a crisis, with incomplete information, and an uncertain future.
- The information provides a view of how diagnostics can be developed in a crisis.
- The questions are considered by a wide range of individuals with different pandemic response responsibilities.
- The information teaches us that, when responding to a novel threat, surveying a number of voices from different vantage points best meets the needs of a global population at risk.
Executive Summary

- RNA (PCR) is preferred analyte type for COVID-19 diagnostic tests; alone or together with antigen and serology
  - Clear call for:
    - Decreased TAT (incl hands-on time, throughput considerations)
    - Increased test performance
    - Increased test access and availability
    - Improvement to supply chain issues, in many cases were limiting throughput
- Great interest in very rapid tests (mins to 2h TAT) for all three analyte types
- Respondents chiefly obtain sample and run directly or utilize central in-house lab
- Facilities chiefly machine capacity or personnel limited (supply chain as well)
- Sample method preference skews towards anterior nasal and saliva
- CRP, D-dimer, Ferritin, LDH, cytokine tests are run to guide treatment/inform prognosis
- Chest X-ray and respiratory infectious disease screening are part of diagnostic package
Executive Summary (cont’d)

- Remaining Challenges: Patient/HCP safety, DDx, Specimen type, Testing venue, Disease Pathophysiology, Predictive/Risk/Prognosis markers, Contact tracing, Reimbursement, Administrative challenges

- (Near) Future Challenges: Test access, Reimbursement/Cost strategies, Need for broad screening test, Need for faster TAT, higher performing tests, Improved contact tracing and testing, “Accepting the new normal”

- Blue Sky Ideas: Broad test access, DTC contact tracing/testing/reporting, Single Test DDx, Prognostics markers, indicators, and tests, Genomic & Epi Research, Vaccine(s) and therapeutics
Respondent Role

- Physician: 30 respondents
- Clinical Lab Manager: 10 respondents
- Medical Practice Manager: 5 respondents
- Nurse: 5 respondents
- Other: 5 respondents
Work Setting

<table>
<thead>
<tr>
<th>Setting</th>
<th># Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Care</td>
<td>11</td>
</tr>
<tr>
<td>Urgent Care</td>
<td>1</td>
</tr>
<tr>
<td>Emergency</td>
<td>10</td>
</tr>
<tr>
<td>Department</td>
<td></td>
</tr>
<tr>
<td>Covid Clinic</td>
<td>2</td>
</tr>
<tr>
<td>Other (Hospital)</td>
<td>15</td>
</tr>
</tbody>
</table>
Testing Volume Over Time

COVID-19 Testing Volume

Peak | Current

# Respondents

Tests/Day

51+ | 41-50 | 31-40 | 21-30 | 11-20 | 0-10

38, 37 Respondents, Closed Response
Diagnostic Analyte Type

COVID-19 Diagnosis: Analyte Type

<table>
<thead>
<tr>
<th>Analyte Type</th>
<th># Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>15</td>
</tr>
<tr>
<td>Antigen</td>
<td>1</td>
</tr>
<tr>
<td>Serology</td>
<td>5</td>
</tr>
<tr>
<td>NA + Antigen</td>
<td>3</td>
</tr>
<tr>
<td>NA + Serology</td>
<td>15</td>
</tr>
<tr>
<td>NA + Antigen + Serology</td>
<td>2</td>
</tr>
</tbody>
</table>

39 Respondents, Open Response, Single Response
Concurrent Clinical Observations & Tests

Clinical Observations and Tests Run Concurrent with COVID-19 Tests

- Chest X-Ray/Imaging: 50.00%
- Respiratory ID/ID Scan: 30.00%
- Std COVID-19 Symptoms Query: 20.00%
- Cultures: 17.00%
- Travel, Exposure, etc Query: 10.00%
- None: 10.00%

Comments:
See Next Slide

27 Respondents, Open Response, Multiple Response
“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, sob, hypoxemia, rashes, diarrhea, uri, and cough.” Chelsea MA Hospital Physician
Tests Run to Guide Care/Prognosis

Comments:
Added Troponin I, (2)
Added EKG, (2)

24 Respondents, Closed Response, Multiple Response
Molecular Diagnostics: Performance

15 Respondents, Closed Response, Single Response/Category

- Performs as Expected
- Does Not Perform as Expected
- Hands On Time: 0-1h, 1.5h, 5-10h
- Ease of Use: Easy, Medium, Hard

#Respondents
Molecular Diagnostics: Improvement

Molecular Diagnostics: Which Aspect(s) Would You Improve

- Performance
- Hands on Time
- Ease of Use
- Technical Performance
- Other

Other:
TAT; Availability; Throughput; Sensitivity Over Time; Lower Resp Tract Samples

14 Respondents, Closed Response, Multiple Response
Antigen Diagnostics

Antigen Test Use

<table>
<thead>
<tr>
<th></th>
<th># Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>19</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
</tr>
</tbody>
</table>

29 Respondents, Closed Response
Antigen Diagnostics: Performance

Antigen-Based Diagnostics Performance

- **Performs as Expected**: 3 respondents
- **Does Not Perform as Expected**: 2 respondents
- **Hands On Time**:
  - 0-1h: 1 respondent
  - 1-5h: 1 respondent
  - 5-10h: 1 respondent
- **Ease of Use**:
  - Easy: 1 respondent
  - Medium: 1 respondent
  - Hard: 3 respondents

6 Respondents, Closed Response, Single Response/Category
Antigen Diagnostics: Improvement

Antigen-Based Diagnostics: Which Aspect(s) Would You Improve

- Performance
- Hands on Time
- Ease of Use
- Technical Performance
- Other

Comment:
High false negatives (verified by PCR)

5 Respondents, Closed Response, Multiple Response
Serological Diagnostics

Serology Test Use

#Respondents

- No
- Yes

26 Respondents, Closed Response
Serological Diagnostics: Performance

Serology Diagnostics Performance

<table>
<thead>
<tr>
<th># Respondents</th>
<th>Performs as Expected</th>
<th>Does Not Perform as Expected</th>
<th>Hands On Time</th>
<th>Ease of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>0-1h</td>
<td>Easy</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>1.5h</td>
<td>Medium</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>5-10h</td>
<td>Hard</td>
</tr>
</tbody>
</table>

14, 11, 11 Respondents, Closed Response, Single Response/Category
Serological Diagnostics: Improvement

8 Respondents, Closed Response, Multiple Response

Other:
Clear indication for use and clear delineation of clinical meaning; Run in-house; Let physicians have easy access to test
Workflow Bottlenecks

Key Diagnostic Workflow Bottlenecks

<table>
<thead>
<tr>
<th>% Respondents</th>
<th>Supply Chain</th>
<th>TAT</th>
<th>Personnel</th>
<th>Lab Capacity</th>
<th>Machine Throughput</th>
<th>Sample Batching</th>
<th>Sendout Inefficiency</th>
<th>PPE</th>
<th>Convenient Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.00%</td>
<td></td>
<td></td>
<td>20.00%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>40.00%</td>
<td>COVID-19 testing Workflow</td>
<td>Overall Diagnostic/Differential Diagnostic Workflow</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

15, 13 Respondents, Closed Response, Multiple Response
Turn Around Time

Typical COVID-19 TAT

<table>
<thead>
<tr>
<th>Sample Draw to Result Report</th>
<th># Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 hours</td>
<td>2</td>
</tr>
<tr>
<td>3-12 hours</td>
<td>6</td>
</tr>
<tr>
<td>12-24 hours</td>
<td>4</td>
</tr>
<tr>
<td>3-8 days</td>
<td>4</td>
</tr>
</tbody>
</table>

18 Respondents, Closed Response
Rapid TAT Test Impact: NA or Ag

Comments:
Test provider availability would be rate limiting; Neither since most diagnosis is made with cxr, ct-radiology; The rapid test needs to be high performing and preferably saliva or a fingerprick blood. The nasal swabs (ant or post) are notoriously inaccurate because pts hate them and pull away. Many bad tests because pts can't handle 1s of discomfort and no actual sample is obtained but the swab is still sent.

16 Respondents, Closed Response
Rapid TAT Test NA or AG Sensitivity Needed

For This Rapid NA or Ag Test (<2h), What is Lowest Acceptable Level of Sensitivity?

- 99%-90%: 15 respondents
- 89%-80%: 5 respondents
- 70%: 2 respondents
- 50%: 1 respondent

Comment:
Day 0-5 illness: 95%
Day 5-10 illness: 80%
Day 10+ illness: 50%

17 Respondents, Open Response
Rapid TAT Test Impact: Serology

Comments:
It would help, but would also be determined by fast blood draws, labs processing which are not always reliable; No - serology not that helpful in initial diagnostics; Maybe, (1); Not too much (1).

13 Respondents, Closed Response
Interest in POC Serology or Antigen Tests

Comment: (from MGH) Would not be that useful in addition to currently available diagnostics.

16 Respondents, Closed Response
Test Processing

How is Testing Performed

- **Samples collected & tested in-house**: 6 respondents
- **Samples collected in-house and sent to our central lab**: 9 respondents
- **Samples are collected in-house and sent to an outside lab**: 2 respondents
- **Other**: 3 respondents

Other:
Testing is ordered at satellite sites; Samples are NOT collected at our clinic, we must send patients to another site for testing (like a private urgent care).

20 Respondents, Closed Response
Laboratory Type

In-House Laboratory Type

- Rapid tests only: 1 Respondent
- Small laboratory space, POC: 2 Respondents
- Medium Complexity Lab: 5 Respondents
- High Complexity CLIA Lab: 8 Respondents
- Do not wish to test COVID-19: 1 Respondent
- No Capacity: 1 Respondent

18 Respondents, Closed Response
Laboratory Capacity Governors

Drivers to In-House Laboratory Capacity

- Machine Capacity: 80.00%
- Personnel: 60.00%
- Lack of shift work: 0.00%
- Available necessary reagents: 70.00%

15 Respondents, Closed Response, Multiple Response
Sample Collection

COVID-19 Sample Collection Methods

- **Nasopharyngeal**
- **Anterior nasal**
- **Throat**
- **Saliva**
- **Capillary blood**
- **Venous blood**
- **Plasma/serum**
- **Other**

Bar chart showing the number of respondents for each sample collection method, with a comparison of those with current capacity and skilled personnel to perform vs. those who prefer to perform.

Other: Lower respiratory tract specimens in greater quantity/faster TAT

18 Respondents, Closed Response, Multiple Response
Home Specimen Collection

Comment:
Low - I'm an ER doc, how many times do women do a home pregnancy test and STILL come to the ER to confirm?

19 Respondents, Closed Response
Analyte Test Bundling

If you could bundle analytes into a single test, which would you bundle?

- Respiratory ID panel: 5
- Infectivity potential: 1
- Ag, Ab: 1

7 Respondents, Open Response
Contact Tracing

Does Your Facility Perform Contact Tracing?

- Yes: 16 respondents
- No: 24 respondents
- No Answer: 16 respondents

16 Respondents, Closed Response
Respondents were asked to comment on unmet clinical needs/use cases for COVID-19 diagnosis, unmet test attributes, remaining challenges.

Beyond *repeated* calls for increased test performance, decreased TAT, resolution of supply chain, test access issues, interesting comments to note:

<table>
<thead>
<tr>
<th>Category, (Frequency)</th>
<th>Comments/Calls</th>
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<tbody>
<tr>
<td>Patient/Practice Safety; PPE (4)</td>
<td>“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”</td>
</tr>
<tr>
<td>Specimen Type (3)</td>
<td>“Need saliva or rapid fingerprick blood testing”; “A sample type that is not the nasopharyngeal”</td>
</tr>
<tr>
<td>Venue (3)</td>
<td>“Rapid testing that is accurate and done at home”; “Rapid POC 15-30’ test with low false negative rate”</td>
</tr>
<tr>
<td>Understanding COVID-19 Disease Manifestation (2)</td>
<td>“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”</td>
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</tbody>
</table>
Respondents were asked to comment on unmet clinical needs/use cases for COVID-19 diagnosis, unmet test attributes, remaining challenges.

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<th>Comments/Calls</th>
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<tr>
<td>Reimbursement/Free Testing (2)</td>
<td>“COVID-19 testing should be free for all at all locations”; “Must address reimbursement, administration support, complete indifference”</td>
</tr>
<tr>
<td>Contact /Asymp Testing (2)</td>
<td>“Testing contacts of all patients who test POS”; “Tests for asymptomatic pts with contacts to COVID”</td>
</tr>
<tr>
<td>Test Admin Time-Consuming (1)</td>
<td>“The lab TAT is long; acquisition is time consuming for staff”</td>
</tr>
<tr>
<td>Electronic Medical Report (1)</td>
<td>“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”</td>
</tr>
</tbody>
</table>
Respondents were asked to comment on the need for predictive or prognostic information not available now would be helpful in the management of COVID-19 patients (i.e. biomarkers, risk factors, etc.)

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<th>Comments/Calls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms/Progression (6)</td>
<td>“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”</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Category, (Frequency)</th>
<th>Comments/Calls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk (2)</td>
<td>“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”</td>
</tr>
<tr>
<td>Miscellaneous (4)</td>
<td>“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.”</td>
</tr>
</tbody>
</table>
Respondents were asked to comment on what do they foresee will be the biggest diagnostic challenges for COVID-19 over the next year.

<table>
<thead>
<tr>
<th>Category, (Frequency)</th>
<th>Comments/Calls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests: Access, Performance, Supply, TAT (7)</td>
<td>“Access to testing, accuracy of testing”; “Speed of testing /results”; “TAT”; “Getting enough testing done (3)”; “Rapid diagnostics of multiple pathogens “</td>
</tr>
<tr>
<td>Differential Diagnoses (6)</td>
<td>“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”</td>
</tr>
<tr>
<td>Miscellaneous (5)</td>
<td>“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 &gt;90 days), how to interpret positive molecular test in the setting of remote antibody positivity (re-infection?)”; “Accepting the new normal”</td>
</tr>
<tr>
<td>Screening (4)</td>
<td>“Prevention and screening”; “Population screening”; “The amount of asymptomatic patients “; “100% sensitivity/specificity for detecting live virus in all people”</td>
</tr>
</tbody>
</table>
Respondents were asked to comment on their "wish list" or "blue sky" ideas, encouraged to be expansive in their thinking.

<table>
<thead>
<tr>
<th>Category, (Frequency)</th>
<th>Comments/Calls</th>
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</thead>
<tbody>
<tr>
<td>Treatment/Prevention (5)</td>
<td>“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)”</td>
</tr>
<tr>
<td>Diagnosis/Differential Diagnoses (3)</td>
<td>“One swab, any type that would run a full viral panel on one sample with a turnaround time &lt;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”</td>
</tr>
</tbody>
</table>
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<thead>
<tr>
<th>Category, (Frequency)</th>
<th>Comments/Calls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology/Research (3)</td>
<td>“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”</td>
</tr>
<tr>
<td>Access, Protocol (2)</td>
<td>“Test every patient admitted to hospital or had a perform procedure”; “Testing available on every corner for free in an urban area”</td>
</tr>
</tbody>
</table>