Diagnostics: Key to the Beginning, Middle and End of the COVID 19 Pandemic

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The Devasting Impact of COVID-19

The Virus vs. The Disease

SARS-CoV2 Virus

COVID-19 Disease

Source: The Lancet Infectious Diseases 2020 20425-434DOI: (10.1016/S1473-3099(20)30086-4)
Everyone wants diagnostics…

Coronavirus Update: Medical Professionals Say They Still Don’t Have Enough COVID-19 Tests To Meet Demand

April 9, 2020 at 11:37 pm  Filed Under: Coronavirus, COVID-19, Jessica Layton, Local TV, New Jersey, Phil Murphy

National shortages threaten COVID-19 testing while scientists try to get needed resources

Alessandro Marezi Sassoon, Florida Today  Published 11:39 a.m. ET March 19, 2020 | Updated 6:56 p.m. ET March 21, 2020

The Real Tragedy of Not Having Enough Covid-19 Tests

The New York Times

Opinion

Coroners worry Covid-19 test shortages could lead to uncounted deaths

By Blake Ellis, Melanie Hicken and Ashley Fantz, CNN Investigates  Updated 10:33 AM ET, Tue April 7, 2020

Coronavirus tests: researchers chase new diagnostics to fight the pandemic

WHY WIDESPREAD CORONAVIRUS TESTING ISN’T COMING ANYTIME SOON

By Robert P. Baird
Three Months since Virus Sequenced

Dx Testing

- SARS-CoV2 Genome Sequence announced 1/11/20
- 1st week CDC performs 100 Dx/day
- CDC distributes flawed Dx
- CDC opens testing to State Health Labs
- FDA releases constraints for antibody testing

November
- 11/17/19 1st Hubei case (unreported)

December
- 1st report from Wuhan

January
- 1st US case
- Disease named COVID-19

February
- 1st US death
- WHO declares pandemic

March
- US declares Federal emergency
- Wuhan re-opened

April
- >2 Million infections

Epidemiology

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Unprecedented # of Tests

Source: Health Catalysts Group analysis

- **Technology**
  - Viral RNA
  - RNA rtPCR

- **Target**
  - Antibody
  - IgM/IgG
  - Viral Ag
  - RNA novel

- **Source Country**
  - Europe
  - Other Asia
  - China
  - US
  - ROW

Source: Health Catalysts Group analysis
### Policy/Recommendation Highlights

<table>
<thead>
<tr>
<th>Policy</th>
<th>Applicable technologies</th>
<th>Validation?</th>
<th>Notification to FDA</th>
<th>EUA to FDA after testing initiated?</th>
<th>Location of Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy A</td>
<td>molecular, antigen, antibody</td>
<td>Yes</td>
<td>From high complexity lab</td>
<td>Yes</td>
<td>High complexity labs only</td>
</tr>
<tr>
<td>Policy B</td>
<td>molecular, antigen, antibody</td>
<td>Yes</td>
<td>From State; encouraged from labs</td>
<td>Not required</td>
<td>High complexity labs in certain states only</td>
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<tr>
<td>Policy C</td>
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<td>Yes</td>
<td>From manufacturer</td>
<td>Yes</td>
<td>Clinical labs or point of care; not for home use</td>
</tr>
<tr>
<td>Policy D</td>
<td>antibody</td>
<td>Yes</td>
<td>From developer (manufacturer or high complexity lab)</td>
<td>Not required</td>
<td>Clinical labs or point of care; not for home use</td>
</tr>
</tbody>
</table>

Source: FDA Weekly Town Hall Webinar 4/1/20
If there are so many tests – why can’t I get one?

- What is the difference between a test for the virus and a test for antibodies for the virus?
- Does it matter if I use a nasal or oral swab; or a spit or sputum; or blood sample?
- How do we use testing to reopen society?
Two Different Questions require Two Very Different Tests

Do I have COVID-19? Active Infection: Symptoms +14 days Am I immune to SARS-CoV2?

The Virus
- Is the virus present?
  - Viral RNA
  - Viral Proteins

Me
- Do I have antibodies to fight off this virus?
  - During Symptoms
  - Before and/or After

Sensitivity Critical
Never miss a case
(no false negatives)

Specificity Critical
Immune really means Immune
(no false positives)
Two Different Questions require Two Very Different Tests

Do I have COVID-19?
Active Infection: Symptoms +14 days
Am I immune to SARS-CoV2?

The Virus
Is the virus present?
Viral RNA
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RNA genome => Virus present
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During Symptoms

IgM => Infection active
IgG => Defense building
IgG:IgM ratio => Stage of recovery
Total Antibody => Criticality

Before and/or After

IgG => Antibody present
Defensive immunity but:
• How long for?
• How effective?

*sub genomic RNA: small messenger RNA’s the virus forces the host cell to make to create essential Virus proteins (rarely clinically tested)
In COVID-19: IgG rises slowly, Virus active longer

Note: Inpatient 2/6-2/14 PLA Central Command Hospital (n=238 symptomatic patients: 153 rtPCR+; 85 rtPCR-); total Ab stays high in all critically ill and terminal patients)
A wide range of technologies (examples)

**Do I have COVID-19?**

**Active Infection: Symptoms +14 days**

**Am I immune to SARS-CoV2?**

**Nucleic Acid Tests** (rtPCR primarily)

- Central Lab automated: *cobas® 6800/8800 System*
- CDC-type rtPCR lab kit (manual)
- Point of Care Automated: Cepheid Gene Expert, Cue

**Immunooassays** (Serology)

- Generic manual ELISA kit
- Fingerstick Point of Care: Camtech COVID-19 IgM/IgG-Rapid Qualitative Screening test
- Central Lab automated: Luminostics

**Point of Care Automated**

- Camtech COVID-19 RT-qPCR kit
- *Camtech COVID-19 IgM/IgG Rapid Qualitative Screening test*
Pros and cons of the Different Tests

**Do I have COVID-19?**

Active Infection: Symptoms +14 days

**Am I immune to SARS-CoV2?**

### Nucleic Acid Tests (rtPCR primarily)
- Swabs are non-invasive
- Exquisitely sensitive and specific
  - ~100 viral copies when positive swabs have 300,000+ copies
  - But:
    - Sampling Hard - Virus is primarily in the lung
      - Nasal and Oral swabs may not reach deep enough
      - Saliva collects more material but is virus captured?
      - Sputum is good, but patients rarely have wet cough
    - Cross-patient contamination at sampling will yield false positives
    - Central Lab takes a minimum of 24 hours mostly longer
    - Inflammatory storm cannot be detected this way and may occur after viral load declines

### Immunoassays (Serology)
- Needs blood serum tube or a fingerstick for POC tests
- Sampling technique variation not an issue
  - But:
    - Antibody design is both an art and a science
      - Vast range of effectiveness for different tests
      - Few companies disclose scientific details
      - 40-90% accuracy
      - Cross-reactivity to similar prior diseases can result in false claims of immunity (IgG is present for years)
      - False positives dangerous, especially for health care workers
      - Immunity value of IgG is unknown (time & effectiveness)
Do I have COVID-19 now?

Effective Sample Taking is Critical

Success Rate in Confirmed Patients*:

- OPS (OroPharangeal Swab): 32%
- NPS (NasalPharangeal Swab): 63%
- Sputum: 90% BUT need productive cough
- BAL (Broncho-Alveolar Lavage): 100% BUT invasive
- Saliva?

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*Source: Wang et al, JAMA March 11, 2020
Not just which test but how the sample is taken

Source: Hsih W-H et al., Journal of Microbiology, Immunology and Infection, https://doi.org/10.1016/j.jmii.2020.03.008
Need Test that is Unique & Essential to SARS-CoV2

SARS-CoV2

ORF1a   ORF1b   S   3a   N

Replication functions

Structural Proteins

96% Bat CoV RaTG13

Horseshoe Bat

% Similarity

Genome nucleotide position

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Need Test that is Unique & Essential to SARS-CoV2

SARS-CoV2

ORF1a  ORF1b

Replication functions

S 3a N

Structural Proteins

SARS-CoV2

96% Bat CoV RaTG13

80% 2002 SARS

Am I immune to SARS-CoV2?
United States: Tests Run Per Day and Positivity Rate

Source: Barclays Research, [https://covidtracking.com/data/us-daily](https://covidtracking.com/data/us-daily)
The Immense Dx Challenge

Do I have COVID-19?

Acute Viral infection
40 Million Tests @ $90 = $3.6 B

Am I immune to COVID-19?

Antibodies to SARS-CoV2
400+ Million Tests @ $40 = $16 B

$20 Billion cost vs. $2.5 Trillion GDP per month

Source: Adapted and updated from “Why We Don’t Know How Many Americans Are Infected With Coronavirus—and Might Never Know”. WSJ 4/4/20
What should be done going forward?

1. Testing must increase 10-fold from current levels
   - Widely available tests with validation data with active CDC/FDA policing for defective or misleading claims
   - All testing must be free to all
   - Consumer Viral and Antibody self sampling and full at home kits needed ASAP

2. Effective treatment protocols established
   - Nationwide data collection on current hospital practices - integration with implications rapidly disseminated
   - Adaptive clinical trials (like NCI MATCH basket trials) with Phase IV type data collected

3. Effective case and positive contact tracing
   - Isolation based on comprehensive contact tracing (Smart Phone enabled)

4. Intelligent, focused quarantine & isolation practices
   - Patient segmentation (recovered, immune, age, existing co-morbidities)
   - SMSA / County specific

5. Hospitals to be re-engineered for adaptability to infectious disease surges
Thank you

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Simplified COVID-19 pathology

Day 1 Virus Binds epithelial cell ACE2 receptor

1-10,000 Virions released to local tissue

Lack of ACE2 constricts blood vessels

Cell no longer able to transport O₂

Blood pressure rises to compensate

Heart stressed to increase O₂ delivery

Exhausted Cell dies 12-24 hours later

Immune system over-reacts

Heart Failure

Multiple organ failure

Death

Hijacks Lung Cell

Immunity