COVID-19 Diagnostics

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April 28, 2020
COVID-19 Timeline

• December 31, 2019 - A pneumonia of unknown cause detected in Wuhan, China first reported to the WHO Country Office in China

• January 30, 2020 – The outbreak was declared a Public Health Emergency of International Concern

• January 31, 2020 - Secretary Azar Declares Public Health Emergency for United States for 2019 Novel Coronavirus

• February 11, 2020, WHO announced a name for the new coronavirus disease: COVID-19
The State of Testing in US and Globally
COVID-19 Testing in the US

Dec 31
WHO reports cluster of cases of pneumonia in Wuhan, China

Jan 20
First confirmed COVID-19 case in US

Jan 17
WHO releases a protocol for RT-PCR testing

Jan 24
CDC announces a test to be distributed with FDA permission

Jan 20
First confirmed COVID-19 case in US

Early Feb
Stanford develops a test but cannot utilize it due to FDA regulations

Feb 12
CDC publicly discloses issues with its test

Feb 4
FDA formally approves CDC's test

Feb 28
Clinical microbiologists complain to Congress about FDA EUA restrictions

Feb 29
FDA eases EUA restrictions. US has first COVID-19 death

Mar 9
Quest begins testing

Mar 5
LabCorp begins testing

Mar 16
FDA announces serological tests may be distributed without approval

Mar 31
US has reached 1 million cumulative tests

Apr 16
91.6% of testing is done by private labs on this day
Number of specimens tested for SARS CoV-2 by CDC labs (N= 5,228) and U.S. public health laboratories* (N= 486,587)†

April 16th, 2020
- 91.6% of testing was done by private labs on this day.
- CDC reported 13,355 tests between its own lab and public health labs.
- Total reported nationally was 158,463.

Note: As of March 12, the dates associated with the specimens tested by CDC Labs have been updated to reflect the date the specimen was received by CDC, instead of when they were collected from the patient. Use of the specimen received date better reflects when specimens became available for testing by the CDC Labs.
Daily tests per thousand people

The 3-day rolling average of the daily number of tests for COVID-19 per thousand people of the country’s population. Given in terms of the number of days since the total confirmed cases reached 1 per million.

Source: Official data collated by Our World in Data, European CDC - Situation Update Worldwide. OurWorldInData.org/coronavirus • CC BY
Note: For testing figures, there are substantial differences across countries in terms of the units, whether or not all labs are included, the extent to which negative and pending tests are included and other aspects. Details for each country can be found at the linked page.
Daily confirmed COVID-19 cases

The number of confirmed cases is lower than the number of total cases. The main reason for this is limited testing.

Source: European CDC – Situation Update Worldwide – Last updated 28th April, 11:30 (London time)
OurWorldInData.org/coronavirus • CC BY
Molecular Testing

• March 12-April 28, 2020 – Thirteen automated integrated diagnostic tests for SARS-CoV-2 testing, 5 modular cartridge based devices (4 of which are designed to be used at POC)

- **Abbott ID NOW**
  - 13 minutes
  - Sensitivity lower with VTM
  - Direct inoculation of swab
  - Popular in US for flu

- **Mesa Biotech Accula**
  - 30 minutes
  - No international usage

- **Biofire Filmarray**
  - 1 hour
  - Has been used internationally for acute febrile illness and respiratory infection

- **Cepheid Xpert Xpress**
  - 45 minutes
  - Massive global penetration due to TB usage and concessional pricing

- **bioMerieux Biofire Filmarray**
  - 1 hour
  - Has been used internationally for acute febrile illness and respiratory infection
<table>
<thead>
<tr>
<th>Company</th>
<th>Gene target</th>
<th>Verified LOD (copies/reaction)</th>
<th>Avg CI (lowest dilution 10/10)</th>
<th>Clinical sensitivity (50 positives)</th>
<th>Clinical specificity* (100 negatives)</th>
<th>Product No.</th>
<th>Product name</th>
<th>Lot No.</th>
<th>PCR platform</th>
<th>Supplier recommended Ct cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>KH Medical Co. Ltd</td>
<td>S</td>
<td>1–10</td>
<td>37.94</td>
<td>100% (95% CI: 93, 100)</td>
<td>100% (95% CI: 96, 100)</td>
<td>RADI COVID-19</td>
<td>uqPCR 200002</td>
<td></td>
<td>BioRad CFX96</td>
<td>≤40</td>
</tr>
<tr>
<td>R-Biopharm AG</td>
<td>RdRP</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Roche LightCycler 480</td>
<td>≤41</td>
</tr>
<tr>
<td>SD Biosensor Inc.</td>
<td>E</td>
<td>1–10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BioRad CFX96</td>
<td>≤40</td>
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<tr>
<td>Seegene Inc.</td>
<td>E</td>
<td>1–10</td>
<td></td>
<td></td>
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<td></td>
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<td>Roche LightCycler 480</td>
<td>≤40</td>
</tr>
<tr>
<td>Tib Molbiol</td>
<td>RdRP</td>
<td>1–10</td>
<td>33.34</td>
<td>100% (95% CI: 93, 100)</td>
<td>100% (95% CI: 96, 100)</td>
<td></td>
<td></td>
<td></td>
<td>Roche LightCycler 480</td>
<td>≤40</td>
</tr>
</tbody>
</table>

* Further investigation needed to determine if apparent false positives are truly false positives or whether they are due to a false negative reference standard result.

SARS-CoV-2 Complete Genome (29903 Nucleotides)

For questions relating to the evaluation of molecular tests, please contact our Emerging Threats team.
Global Issues with COVID-19 Molecular Testing

- Limited Lab Capacity - Only reference labs do RT-PCR testing
  - Countries with strong global health security programs have hub and spoke specimen transport that has been activated for COVID-19
- Nasopharyngeal swabs rarely performed - need to validate sample types including self-collected, oropharyngeal, nasal
- Global swab shortages
- Biosafety concerns with getting samples
- COVID-19 patient disposition – isolation difficult in crowded households
Correlation between viral load and illness severity

• 90% of patients with mild disease tested RT-PCR negative by day 10 after symptom onset
• All patients with severe disease tested positive at or after day 10

Need for molecular capacity everywhere

How does RT-PCR positivity link with culture positivity?
In turn, how does that link with transmissibility?

....stay tuned...
<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Rapid Diagnostic Test (RDT)</th>
<th>ELISA</th>
<th>Neutralization Assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read-out</td>
<td>Qualitative</td>
<td>Qualitative/Quantitative</td>
<td>Quantitative</td>
</tr>
<tr>
<td>How</td>
<td>Point-of-care, lateral flow test, whole blood, plasma, serum</td>
<td>Lab-based test, Binding of patient antibodies to a fixed viral protein, plasma, serum</td>
<td>Lab-based test, cell culture live virus assay that tests ability of the patient antibodies to confer protective immunity</td>
</tr>
<tr>
<td>What</td>
<td>IgM, IgG specific to SARS-CoV-2</td>
<td>IgM, IgA, IgG</td>
<td>Neutralizing titer</td>
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<tr>
<td>Time</td>
<td>10-30 minutes</td>
<td>2-5 hours</td>
<td>3-5 days</td>
</tr>
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</table>
Serological Testing

- Validated tests
  - Only 8 have been approved via FDA EUA, many more globally
  - Detects different antigens (spike 1, spike 2, receptor binding domain, nucleocapsid protein)

Nucleocapsid –
Sensitive, less specific

Spike protein
- Full length spike less specific, more sensitive
- RBD – more specific, less sensitive
How should serological tests be used?

Surveillance to estimate population proportion exposed and previously infected

...but not all tests are created equal
Serological Test Use Cases - individual

- Diagnose infection in patients who are NP swab RT-PCR negative with symptoms for more than 10-14 days.
- Show COVID-19 exposure in a person with a plausible suspected infection in the recent past
  - Essential workers (e.g., healthcare workers, workers that interact with vulnerable populations like nursing homes)
  - Correlation with protective immunity unknown

Parallel or sequential testing...
Issues with Serological Testing

- Antigens have different sensitivity and specificity which is also dependent on timing after infection and the isotype (Zhao J DOI: 10.1093/ciaa344)
- Unclear serological response across patient populations
  - Seronegative patients with RT-PCR evidence of infection: 175 Chinese patients, 30% failed to produce high levels of IgG antibodies, 5% no antibodies (Wu F 2020 https://doi.org/10.1101/2020.03.30.20047365)
April 24, 2020 – WHO virtual COVID-19 meeting

“‘Our shared commitment is to ensure all people have access to all the tools to prevent, detect, treat and defeat COVID-19. No country and no organization can do this alone. The Access to COVID-19 Tools Accelerator brings together the combined power of several organizations to work with speed and scale.’”

Tedros Adhanom Ghebreyesus, WHO Director-General
Life is not about waiting for the storm to pass, but learning to dance in the rain”

---Raila Odinga Inouye