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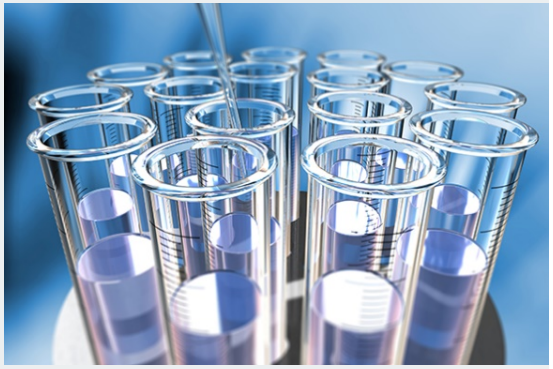


HA101: Demystifying SARS-CoV-2 Testing for COVID-19

Second Edition

Health Advances LLC
BOSTON | SAN FRANCISCO | ZUG | HONG KONG
www.healthadvances.com

What to Expect from These Reports

This document provides a high level, easy-to-read review of

- What testing we need now and in the future to move to a “new normal”
- Why it is challenging to get this testing up and running at volumes needed for the US

What questions do you have regarding SARS-CoV-2/COVID-19 testing?

Please email additional questions to:
diagnostics@healthadvances.com

Agenda

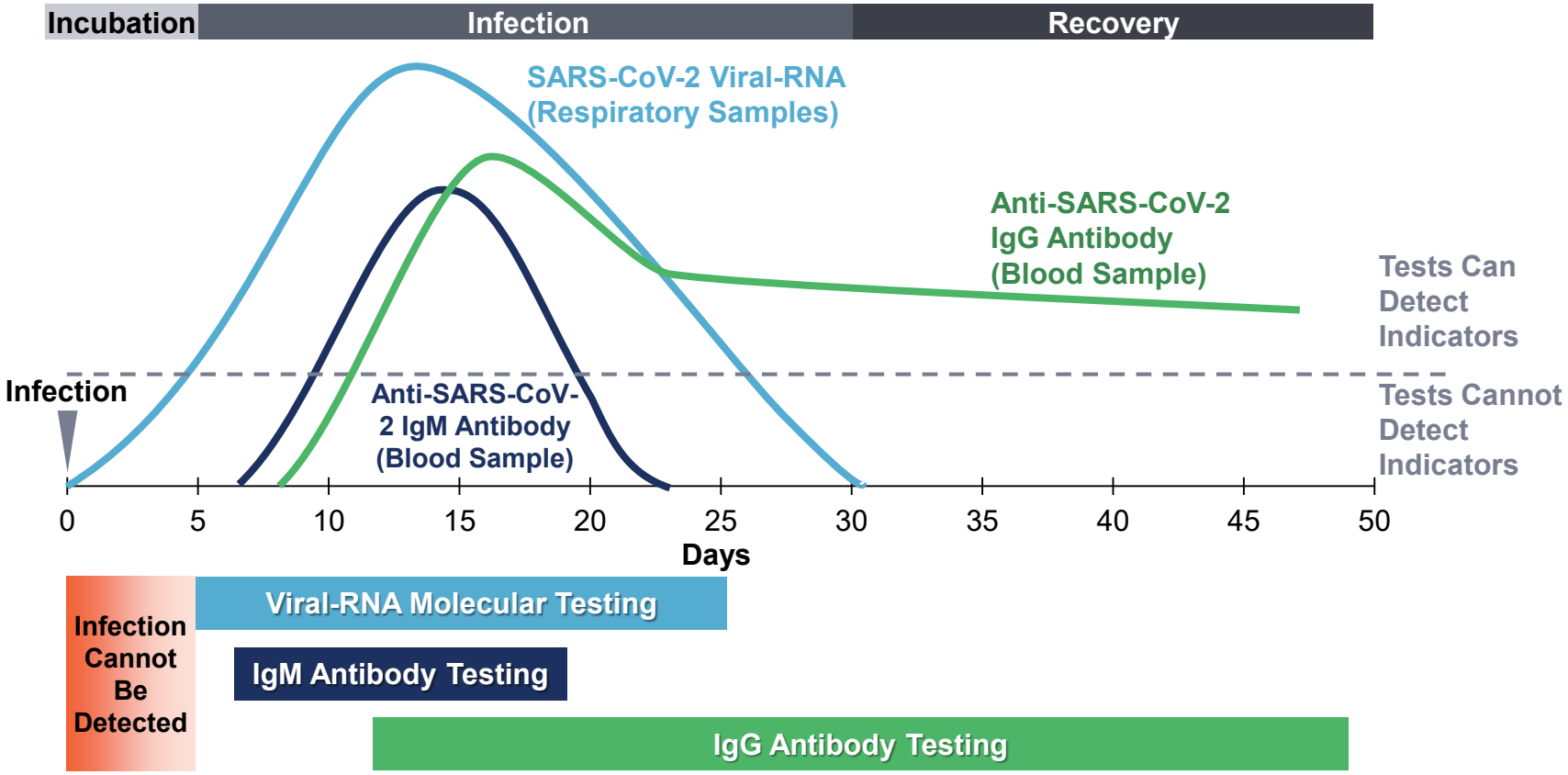
- ***What do we know about markers of disease and recovery for SARS-CoV-2?***
- What types and how much testing do we need now and in the future?
- Why was testing in the US slow to emerge?
- Why is it hard to get testing up and running? How is this different for molecular versus serology?
- What tests are available for SARS-CoV-2 testing in the US today?
- What are the challenges and outlook for the available tests?
- Appendix

Biology of SARS-CoV-2 Infection

A combination of disease biology and test capability dictates if a particular test is useful for assessing current or past SARS-CoV-2 infection.

Markers of Disease by Stage of SARS-CoV-2 Infection

Example Individual Response Based on Best Available Data as of 4/27/2020



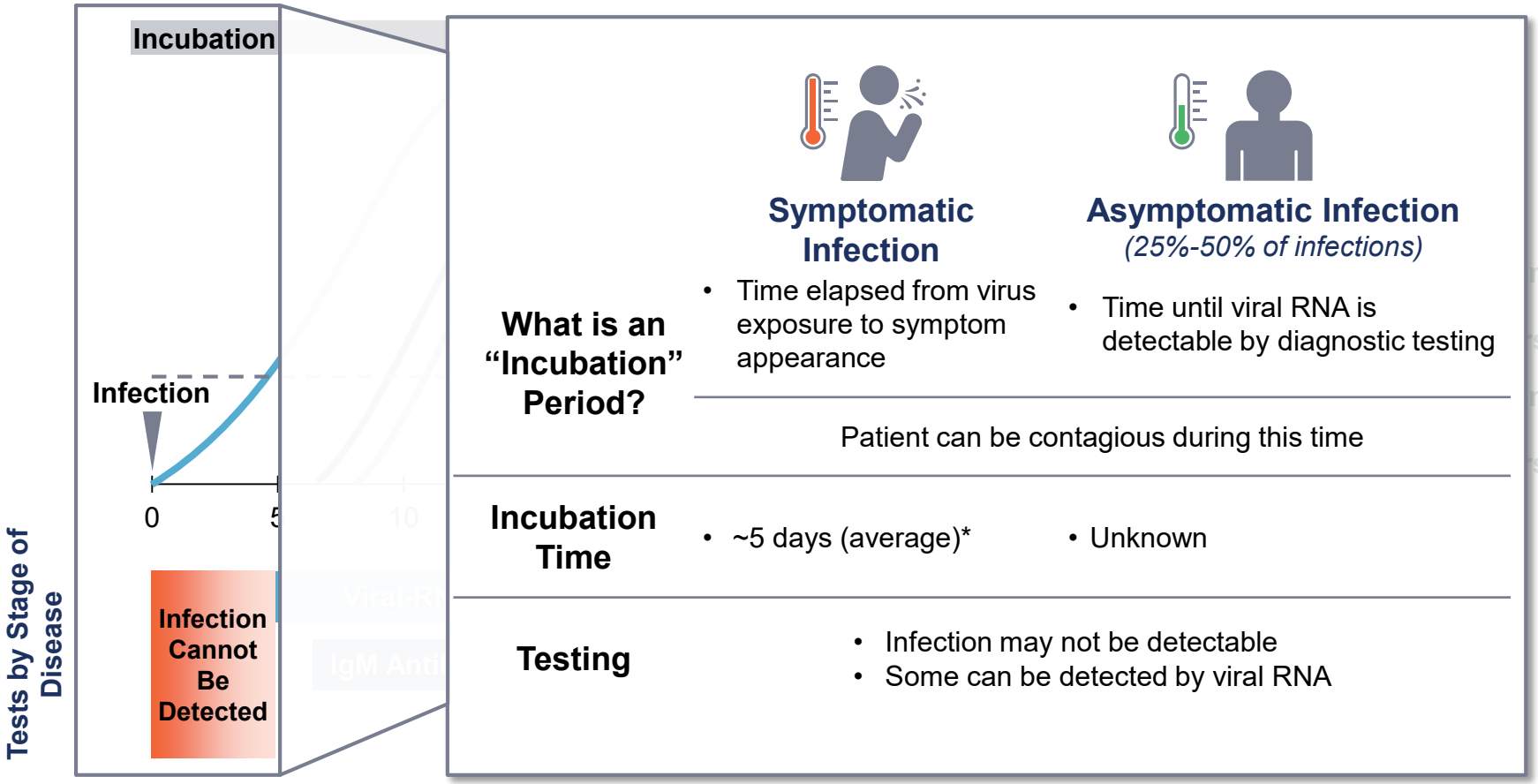
Note: New data (Long 2020 Nature Medicine), not yet confirmed, suggests IgM may not always rise before IgG.
Source: Health Advances analysis, National Academies of Science 2020, Guo 2020 Clin Inf Diseases, Okba 2020 Emerg Inf Disease, He 2020 MedRxiv, Lauer 2020 Annals of Int Med, Kai-Wang 2020 Lancet, Zhao 2020 Clin Infec Disease, Wolfel 2020 Nature.

Infection and Detection During the Incubation Stage

During the incubation period, detection of SARS-CoV-2 infection may not be possible despite infected individuals potentially being contagious.

Markers of Disease by Stage of SARS-CoV-2 Infection

Example Individual Response based on Best Available Data as of 4/27/2020



	Symptomatic Infection	Asymptomatic Infection (25%-50% of infections)
What is an "Incubation" Period?	• Time elapsed from virus exposure to symptom appearance	• Time until viral RNA is detectable by diagnostic testing
	Patient can be contagious during this time	
Incubation Time	• ~5 days (average)*	• Unknown
Testing	• Infection may not be detectable • Some can be detected by viral RNA	

* 97% show symptoms by day 11.5.

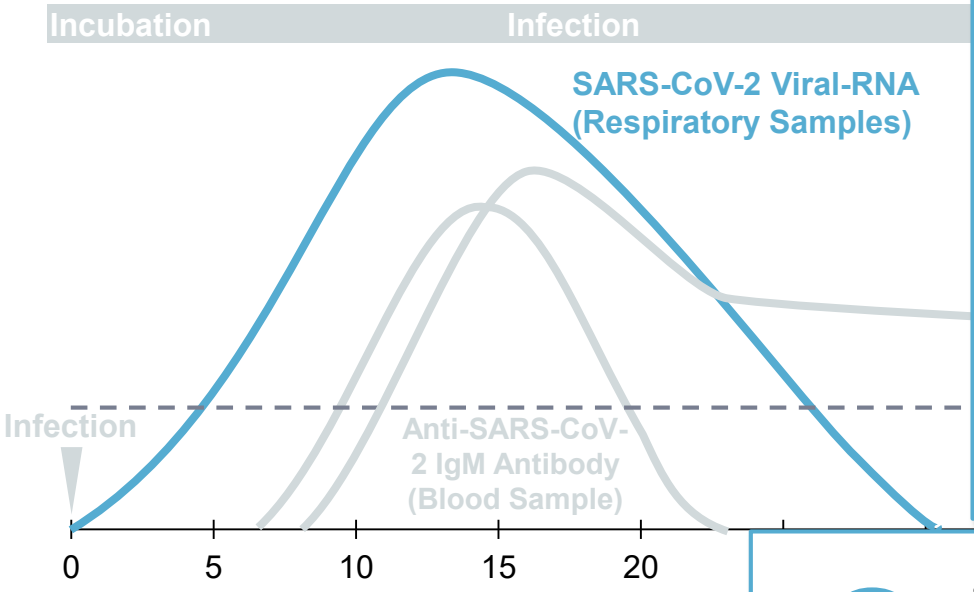
Source: Health Advances analysis, Lauer 2020 Annals of Int Med.

The Impact of Viral RNA Shedding on Infection Tracking

As infection progresses, molecular viral RNA testing is the mainstay of diagnosis though it is not 100% clear if all patient groups are detectable and for how long.

Markers of Disease by Stage of SARS-CoV-2 Infection

Example Individual Response based on Best Available Data as of 4/27/2020



The Amount and Duration of Detectable RNA Can Differ by Patient Group

Lower Virus Amount	*Higher Virus Amount*
Shorter Duration	*Longer Duration*
Mild disease	Severe Disease
Females	Males
Patients <60 yrs	Patients >60 yrs

?

Still Unknown

- Does the amount of viral RNA differ for asymptomatic patients?
- Are there asymptomatic patients without detectable levels of viral RNA?
- How does the amount of RNA correlate with contagiousness?

Note: Virus is "shed" (shedding) as it replicates in the patient.

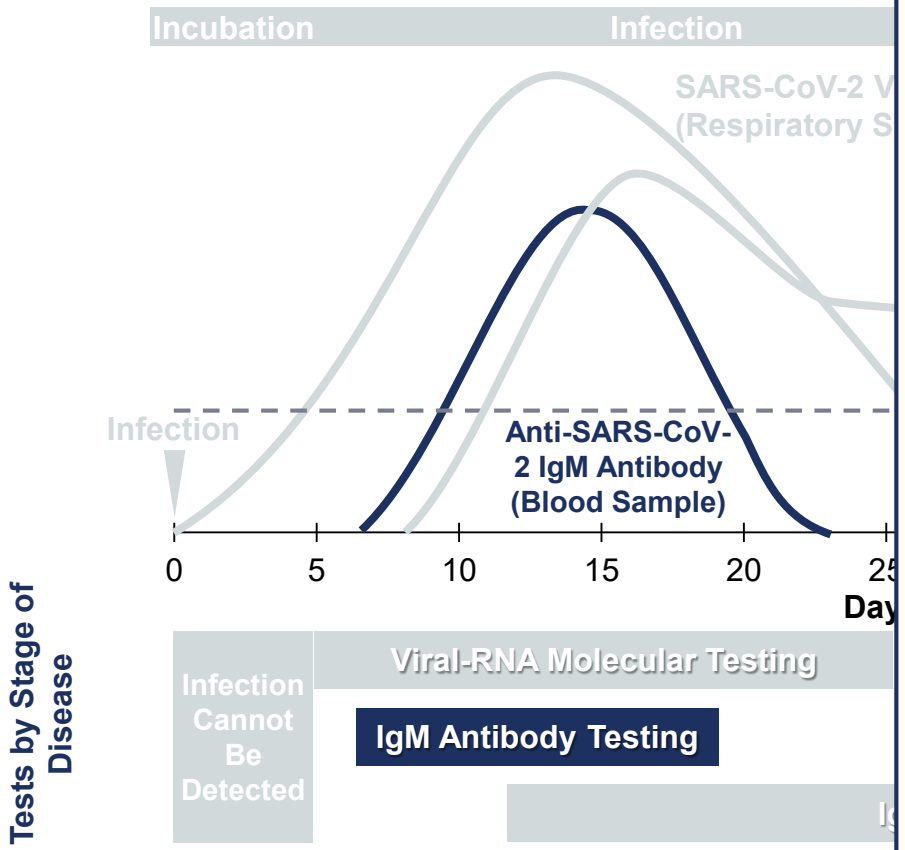
Source: Health Advances analysis, Sherin 2014 Am Fam Physician, Alexander 2016 CVI ASM, Wolfel 2020 Nature, He 2020 MedRxiv, Lauer 2020 Annals of Int Med.

The Role of IgM Antibody Testing on Pandemic Tracking

Given questions about the timing and consistency of IgM antibodies to SARS-CoV-2, the use of IgM alone for diagnosis, screening or surveillance is not advisable.

Markers of Disease by Stage of SARS-CoV-2 Infection

Example Individual Response based on Best Available Data as of 4/27/2020



The Amount of Antibody May Differ by Disease Severity, but Available Data Is Mixed

Less Antibody		*More Antibody*
X		!
Non-critical		Critical

We don't know how antibody titers differ between symptomatic and asymptomatic individuals

Symptomatic Infection

?

Asymptomatic Infection
(Some may not develop antibodies)

New data suggests IgM and IgG may rise simultaneously or IgM may arise later or not at all

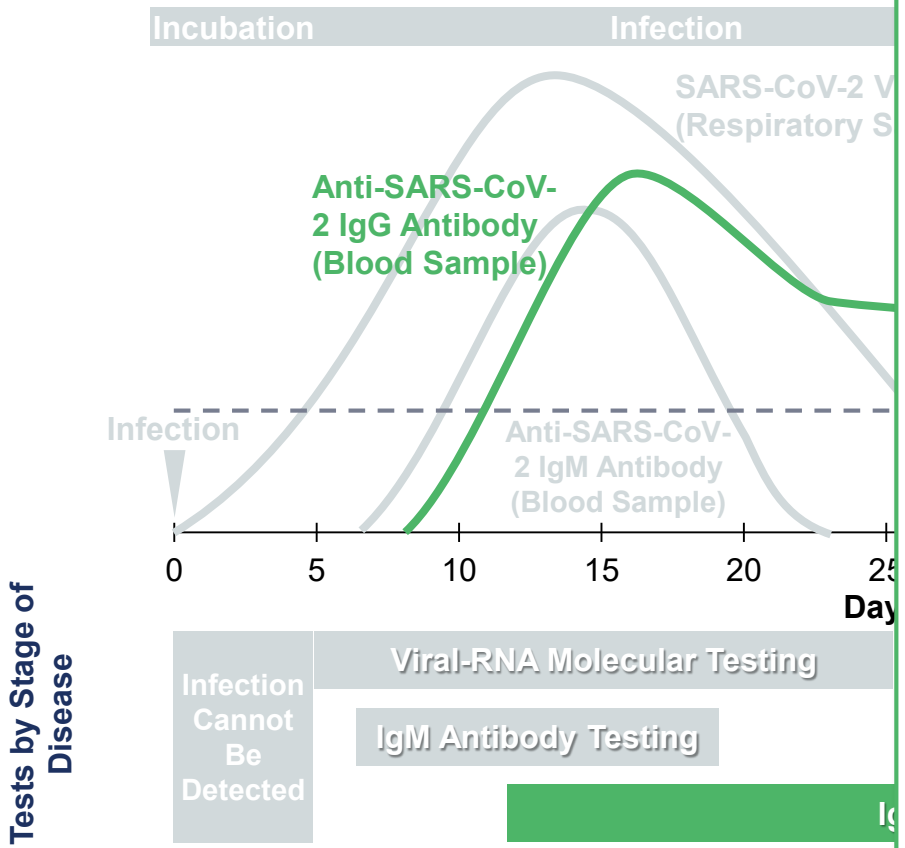
Note: Titer = the amount of (concentration) of antibody in the blood.
Source: Health Advances analysis, National Academies of Science 2020, Guo 2020 Clin Inf Diseases, Okba 2020 Emerg Inf Disease, Zhao 2020 Clin Inf Diseases.

The Role of IgG Antibody Testing on Pandemic Tracking (1 of 4)

IgG typically indicates mature infections. For SARS-CoV-2, IgG may arise early suggesting a total Ig test will be most useful as a complement to viral RNA tests for both diagnostic and surveillance purposes.

Markers of Disease by Stage of SARS-CoV-2 Infection

Example Individual Response based on Best Available Data as of 4/27/2020



The Amount of Antibody May Differ by Disease Severity, but Available Data Is Mixed

Less Antibody		*More Antibody*
X	Non-critical	! Critical
Younger patients		Older patients

We don't know how antibody titers differ between symptomatic and asymptomatic individuals

Symptomatic Infection ? **Asymptomatic Infection**

(Some may not develop antibodies)

New data suggests IgM and IgG may rise simultaneously or IgM may arise later or not at all

Source: Health Advances analysis, National Academies of Science 2020, Guo 2020 Clin Inf Diseases, Okba 2020 Emerg Inf Disease, Zhao 2020 Clin Inf Diseases, Wu 2020 MedRxiv.

The Role of IgG Antibody Testing on Pandemic Tracking (2 of 4)

Anti-virus IgG to SARS-CoV-2 is expected by many to indicate at least some level of immunity. However, in some other infections this is not the case.

Categories of Viruses

by Antibody/Immunity Relationship

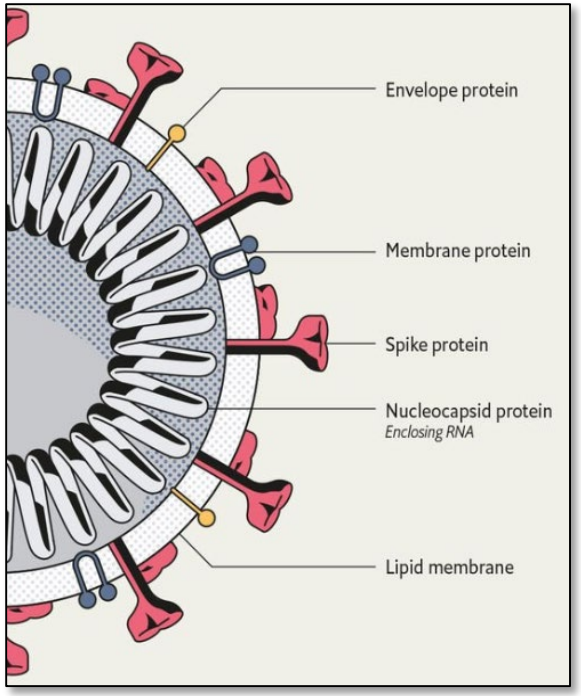
Description	• Any amount of IgG antibody indicates **immunity**	• Only a certain amount of antibody indicates **immunity**	• Presence of antibodies only indicates recent infection or prior exposure, but **not immunity**
Examples	• Hepatitis A • Chicken Pox	• Hepatitis B	• HIV • EBV (Epstein Barr virus) • Flu

Right now, whether antibodies provide future immunity is not definitively proven!

Source: Health Advances analysis, Mayo Clinic.

The Role of IgG Antibody Testing on Pandemic Tracking (3 of 4)

While conclusive data is not yet available, early evidence suggest antibodies to certain parts of the virus provide immunity, suggesting that IgG testing could be used to identify immune individuals.



Antigen	Summary
Spike Protein (S)	• Plays an essential role in viral attachment, fusion, entry, and transmission • Early animal studies show possible immunity against re-infection – S1, S2, and RBD subunits likely target sites for neutralizing antibodies (NAbs) – Only if levels of specific IgG against spike protein are produced at early stage of primary infection
Nucleocapsid Protein (N)	• Structural protein that seems to trigger the production of NAbs, though to date is less studied than the S antigen

According to the WHO, as of April 24 no study has fully evaluated whether the presence of antibodies to SARS-CoV-2 confers immunity to subsequent infection by this virus in humans

Note: RBD = receptor-binding domain. Neutralizing antibodies are what prevent virus from continuing to replicate and cause disease.
Source: Health Advances analysis, WHO, Jiang 2020 Trends Immunol, McKenna 2020 Scientific American, Zhou et al. 2020 Nature, Bao et al 2020 BioRxiv, Wu 2020 medRxiv, Grzelak et al. 2020 medRxiv, Okba 2020 Emerg Infect Diseases, The Economist.

The Role of IgG Antibody Testing on Pandemic Tracking (4 of 4)

How long immunity might last, as measured by IgG, remains uncertain, but will be revealed as the pandemic experience lengthens.

Markers of Disease by Stage of SARS-CoV-2 Infection

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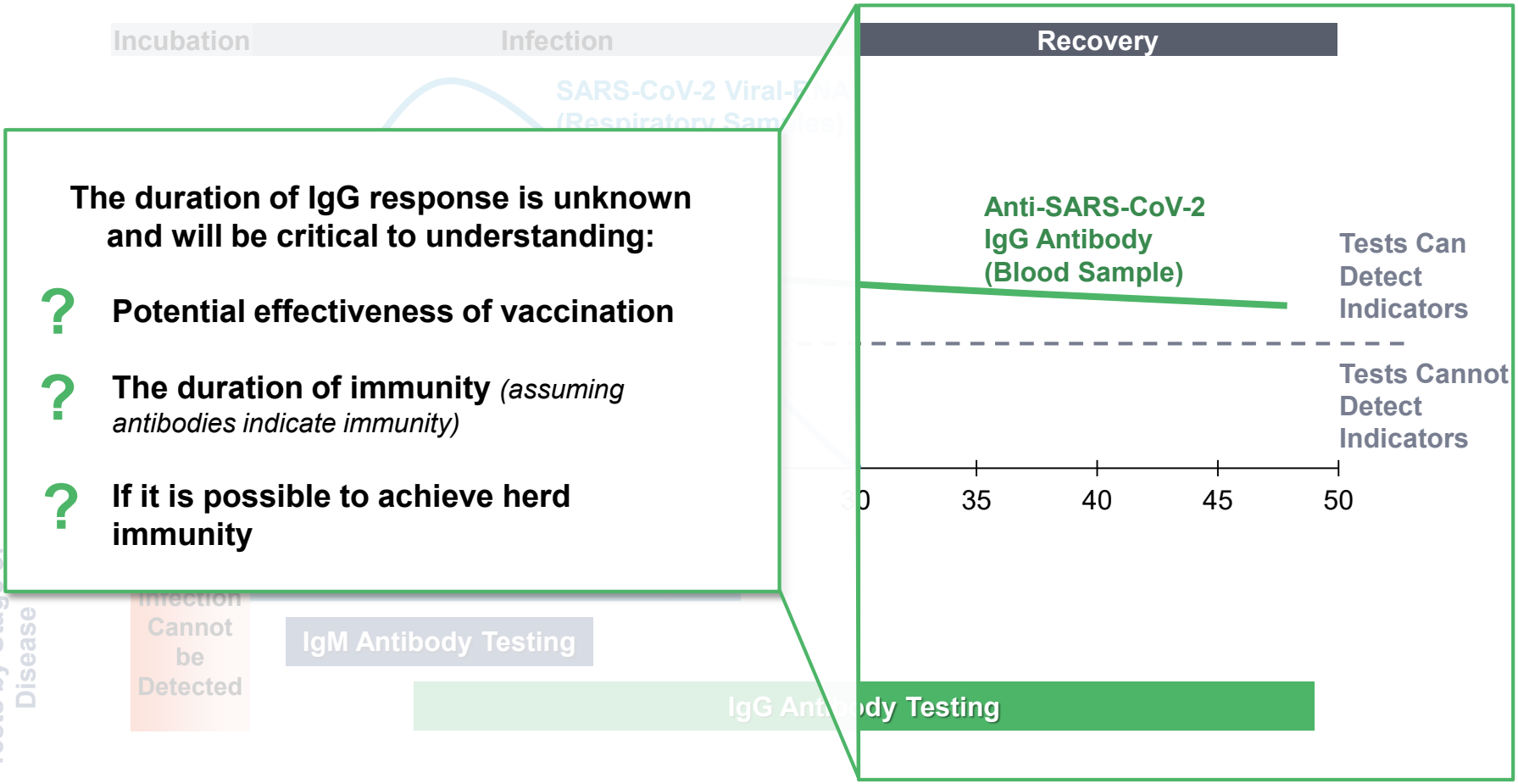

The duration of IgG response is unknown and will be critical to understanding:

- ? **Potential effectiveness of vaccination**
- ? **The duration of immunity** *(assuming antibodies indicate immunity)*
- ? **If it is possible to achieve herd immunity**

Source: Health Advances analysis, National Academies of Science 2020, Guo 2020 Clin Inf Diseases, Okba 2020 Emerg Inf Disease, Zhao 2020 Clin Inf Diseases, Wu 2020 MedRxiv.

Summary of Limitations for Each Test Type

Updated 5/5/2020

Given what we know about disease biology and the fact that we are still on the steep part of the "Rona" learning curve, potential limitations of each test must be recognized..

Test	Type of Risk	Rationale and Other Limitations	
 **IA for IgM**	Missed Infections		• Unlike many other viral infections, not all patients develop IgM at detectable levels • Not as sensitive or specific as molecular for diagnosis and less specific than IgG
 **IA for IgG**	False Conclusion of Immunity	• Not all patients have the same levels, timing or combination of antibody response • Tests available are still being validated and have mixed accuracy	• Unclear of degree or length of immunity if antibodies present • Available tests measure antibodies to different parts of the virus (S v N) with potentially different clinical implications[1]
 **IA for IgA**			
 **IA for Total Ig**			• May be more sensitive but is complex to develop[2] • More costly
 **Molecular for Viral RNA**	Missed Infection Considered Infectious Longer than Necessary	• Negative isn't a guarantee of no infection – Viral load in some samples/ patients may be below detection levels – Not all tests have same sensitivity • Positive doesn't always mean infectious – Evidence of shedding for extended time periods, not all still infectious! – Capacity to perform this type of testing more limited than serology	

[1] Anti-N may be best for sensitivity of detecting past infection/exposure/contact tracing. Anti-S may be needed for detecting those that are immune.
[2] Particularly if all Igs reported separately as well as Total Ig
Source: Health Advances analysis.

Summary of Considerations for Testing Based on Disease Biology

Updated 5/5/2020

What we do know is that no one test will be enough to manage the pandemic.

Test	Strongest Likely Use Case	Rationale
 **Molecular for Viral RNA**	• Use as primary testing tool for diagnosis, screening, surveillance, and tracing	• Least risk of missing an active infection
 **IA for Total Ig**	• Supplement molecular for diagnosis of symptomatic as well as screening, surveillance and tracing	• Most sensitive serology option, but not as sensitive as molecular
 **IA for IgM and IgG Together**	• Supplement molecular for screening, surveillance and contract tracing	
 **IA for IgG Alone**	• Now – Supplement molecular for screening, surveillance and contract tracing • Future – immune status monitoring	• Most consistent single Ig • Timing of presentation similar to IgM
 **IA for IgM Alone**	• Follow-up test in highly suspicious symptomatic cases negative on molecular	• Can be less specific than other Ig • Not sensitive enough to be a diagnostic on its own

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Recovery Over the Course of Different Phases

A multi-phased plan is needed to reopen the economy and establish a new normal.

SARS-CoV-2 Pandemic Recovery and Management Stages

When	**Today**	**Next 1+ Year**	**In 2+ Years**
Goal	**Flatten the Curve**	**Prevent and Manage New Outbreaks**	**Ongoing Management**
Activities	• Reduce spread with social isolation and distancing • Close all non-essential businesses/institutions • Build testing and tracking capabilities and stock of healthcare supplies • Manage healthcare personnel capability	• Reduce social isolation and phase in business activities • Quickly contain outbreaks/ "hot spots" quickly – Aggressive testing and tracing – Sentinel monitoring of at-risk populations – Testing large groups • Develop understanding of disease, epi, and treatment	• Understand the virus and treatment protocols • Establish possible herd immunity and/or vaccine • End social distancing • Manage as an individual disease instead of epidemic • Aggressively pursue outbreak suppression

Source: Health Advances analysis, American Enterprise Institute.

Testing Needs in Phase I: Initial Shutdown

PI → PII → PIII

Testing in Phase I should be focused on diagnosing symptomatic patients, screening essential workers, and high-risk groups, and studying community infection rates.

Patient Group	Test Purpose	Primary Test	Support Tests[1]
 Symptomatic Patients	Detect Active Infection	Molecular for Viral RNA	IA for IgM
 Essential Workers	Screen for Active Infection	Molecular for Viral RNA	IA for IgG +/- IA for IgM
 Select High-Risk Groups[2]	Screen for Active Infection	Molecular for Viral RNA	IA for IgG +/- IA for IgM
 General Population	Study Community Spread	IgG Antibody Test	IA for IgA or Total Ig; Molecular for Viral RNA

[1] Includes confirmation of suspicious or discordant results from the first test.
[2] Includes those exposed to SARS-CoV-2, those with compromised immune systems, and those in high-risk settings (e.g., nursing homes).
Note: IA = immunoassay.
Source: Health Advances analysis.

US Testing Success in Phase I

PI → PII → PIII

In part due to slow ramp-up of testing, to date, testing in the US for Phase I has been more limited than ideal.

Patient Group	Test Purpose	Degree of Testing Occurring	Rationale
 **Symptomatic Patients**	**Detect Active Infection**		• Lack of capacity and sample collection supplies • Limited to sickest patients[2]
 **Essential Workers**	**Screen for Active Infection**		• Lack of capacity and sample collection supplies • Limited to sickest patients[1]
 **Select High-Risk Groups[2]**	**Screen for Active Infection**		• Lack of capacity and sample collection supplies • Difficulty accessing high-risk groups
 **General Population**	**Study Community Spread**		• Initial focus on molecular diagnostic test deployment • Questionable test quality

[1] Eligibility guidelines are expanding.
[2] Includes those exposed to SARS-CoV-2 and those with compromised immune systems, those in high-risk settings (e.g., nursing homes).

Source: Health Advances analysis.

Testing Needs in Phase II: Gradual Re-Opening

PI → PII → PIII

In Phase II, testing will need to continue for Phase I groups while expanding to contact-tracing and screening of larger portions of the population.

Patient Group		Test Purpose	Primary Test	Support Tests
 **Phase I Groups**		Detect Active Infection	**Molecular for Viral RNA**	**IA for IgG** +/- **IA for IgM**
 **Contact Tracing**	**If Contact Symptomatic**	Confirm Active Infection	**Molecular for Viral RNA**	**IA for IgG** +/- **IA for IgM**
	If Contact, Asymptomatic 1-5 Days Post Contact	Screen for Active Infection		
	If Contact, Asymptomatic >5 Days Post Contact	Screen for Active Assess Infection History	**IA for IgG**	**Molecular for Viral RNA**
 **Other Workers and Large Groups[1]**		Screen for Active	**Molecular for Viral RNA**	**IA for IgA or Total Ig** **IA for IgM**
		Assess Immune Status[2]	**IA for IgG**	

[1] Includes schools, certain large employers and those in close living quarters (e.g., nursing homes).
[2] Based on assumption that antibodies do indicate at least some level of immunity.

Source: Health Advances analysis.

Volume of Testing Needed for US Phase II

The capacity of testing needed in the US to re-open is a topic of debate with higher estimates both challenging to meet and likely more effective as control mechanisms.

Projections for Daily Testing Capacity Needed

	Harvard Global Health Institute	Rockefeller Foundation	Harvard Safra Center for Ethics	Paul Romer
Publication(s)	• Why we need at least 500K tests per day to open the economy — and stay open	• National Covid-19 Testing Action Plan	• Why We Must Test Millions a Day – White Paper • Roadmap to Pandemic Resilience	• Roadmap to Responsibly Reopen America
Date Published	• April 18	• April 22	• April 8 and April 20	• April 23

- While larger projections may seem excessive*, consumer demand and employer driven testing to mitigate liability risk are likely to drive need beyond pure clinical rationale
- For most of these projections, the majority of testing is assumed to be by molecular viral RNA methods with immunoassay for assessing immune status as supplementary.

* One reason the US needs more testing is initial viral spread was and is more wide spread than in other regions.

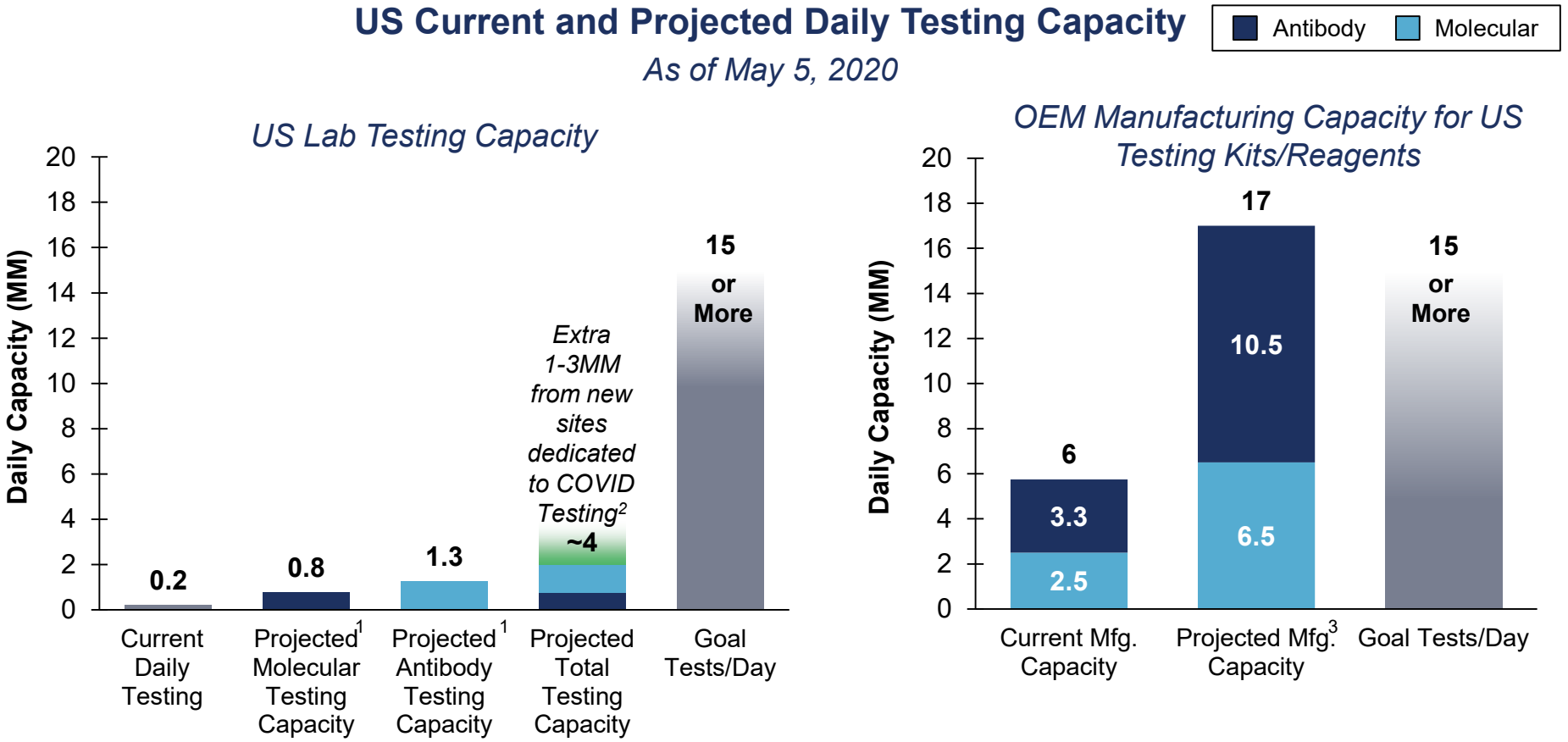
Source: Health Advances analysis, Harvard Global Health, PaulRomer.net, Rockefeller Foundation, Harvard Edmond J. Safra Center for Ethics.

Ability to Achieve Testing Goals

Given current and anticipated testing capacity, the US will need to rely more heavily on a mix of molecular and immunoassay tests, rather than primarily on molecular.

US Current and Projected Daily Testing Capacity

As of May 5, 2020



[1] Projection consider the next several months as a time frame. [2] The Extra 1-3MM capacity is based on other new locations (not current clinical labs) for testing expected to become available, such as employer-based testing; research lab capacity shifts, additional commercial specialty lab capacity conversions etc.. [3] Projection will ramp quickly over the next few months but not fully reach these numbers until end of 2020.

Note: All projections are compiled from the combined stated numbers for larger labs and manufactures with scaling based on Health Advances analysis of relative capacity among smaller platers and the number of labs and OEMs offering or projected to offering testing or manufacturing. OEM manufacturing capacity for RNA and immunoassay tests considers all manufacturers that have notified the FDA and made their tests available for purchase in the US. This manufacturing capacity represents only what we estimate will be available in the US, and not global manufacturing capacity.

Source: Health Advances analysis, company websites, press releases, COVID Tracking Project.

NIH Initiative for Accelerated Development of SARS-CoV-2 Tests

The NIH, recognizing the need for millions of tests per week, has launched a program to help accelerate test development.

National Institute of Allergy and Infectious Diseases

- Announced April 29, 2020
- $1.5B initiative*
- Goal: Speed development/commercialization of accurate tests such that by end of summer/fall 2020, "millions of tests per week" will be deployed

- Focus on **rapid testing technology**
- Best/selected candidates with "**very high sensitivity and specificity" for at-home or POC tests for Sars-CoV-2**
- **Initial review for technical, commercial, and regulatory issues**:
  - Testing technology scalability
  - Advantages over existing approaches
  - Likelihood for US adoption

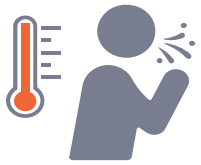
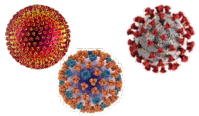
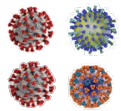
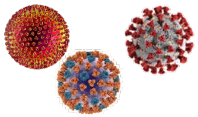
- Winning technologies will feature the following for **POC/at-home testing**:
  - Patient-friendly designs
  - Mobile-device integration
  - Affordable cost
  - Increased accessibility
- Finalists get **"fast track" approval process**
  - Also paired with technical, business, and manufacturing experts to facilitate commercialization

* Called the Rapid Acceleration of Diagnostics (RADx).
Note: POC = point of care.
Source: Health Advances analysis, NIH, GenomeWeb.

Testing Needs in Phase III: Eventual Steady-State

PI → PII → PIII

If successful in Phase I and II, then eventually we may learn enough about the virus, while having it contained, to manage it similar to flu but with contact tracing as well.

Patient Group	Diagnostic Purpose	Primary Test	Support Tests
 Symptomatic Patients	Detect Active Infection	 Flu, RSV, Rona RNA Mini Panel	 Broad Respiratory RNA Panel Test  Immunoassay for Viral Proteins*  Molecular for Viral RNA  IA for IgG  IA for IgM
 Contact Tracing	Screen for Active Infection and Immune Status	 Molecular for Viral RNA	 Flu, RSV, Rona RNA Mini Panel  Immunoassay for Viral Proteins*  IA for IgG  IA for IgM

* May be particularly important for geographic regions (in and outside the US) with lack of access and capability to perform molecular testing.

Source: Health Advances analysis.

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Differences in SARS-CoV-2 Testing Response Timelines

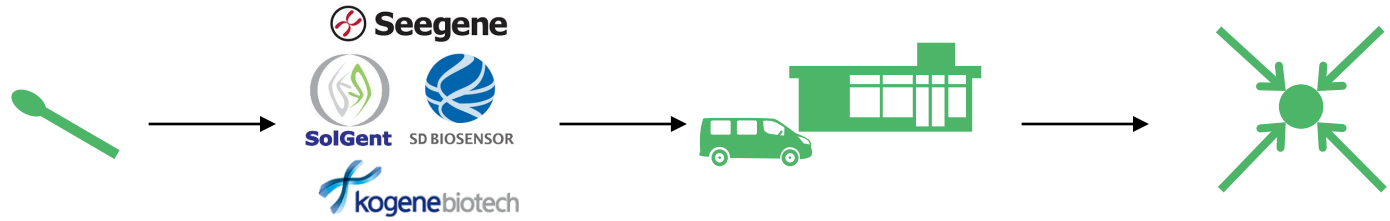
Although both countries had their first confirmed cases on the same day, South Korea more aggressively sought development, approval, and use of SARS-CoV-2 testing than the US.

Note: Current research suggests the UK did not publicly engage with private diagnostic companies during this timeframe.
Source: WHO, FDA, CDC, KCDC, Robert Koch Institute, John Hopkins CSSE.

South Korea and Germany Testing Strategies

South Korea implemented a centralized approach to the implementation of widespread testing. Germany utilized its laboratory expertise to implement decentralized testing.

The South Korean Centralized Approach



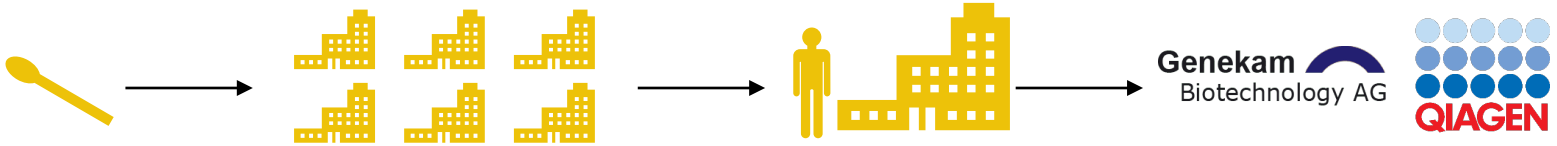
WHO Validated Test Kit

KR Government engaged with 4 manufacturers in Jan. to replicate the WHO kit

Set up drive-through clinics to enable access to testing in January

Directed test kits to hotspots within the country

The German Decentralized Approach



WHO Validated Test Kit

In January, Germany authorized hundreds of labs to develop LDTs, implementing virology expertise to replicate the WHO kit

Patients could access the closest hospital for testing

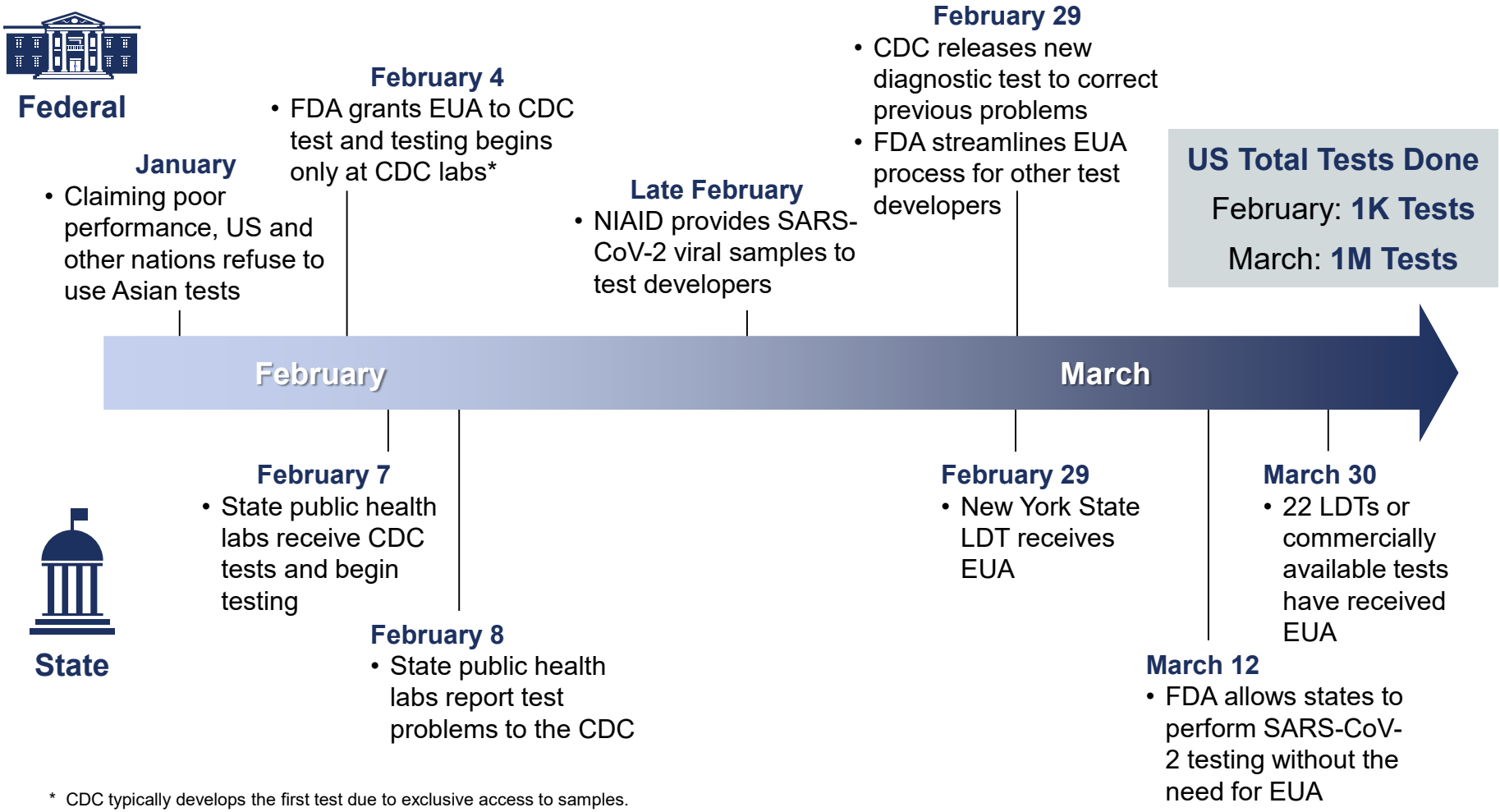
Germany then authorized commercial testing kits for scale-up in early February

Source: Health Advances analysis.

What Was the Hold Up with SARS-CoV-2 Testing in the US?

US

Building SARS-CoV-2 diagnostic testing capacity was a slow process in the US, initially due to CDC test kit manufacturing issues and FDA red tape.



* CDC typically develops the first test due to exclusive access to samples.

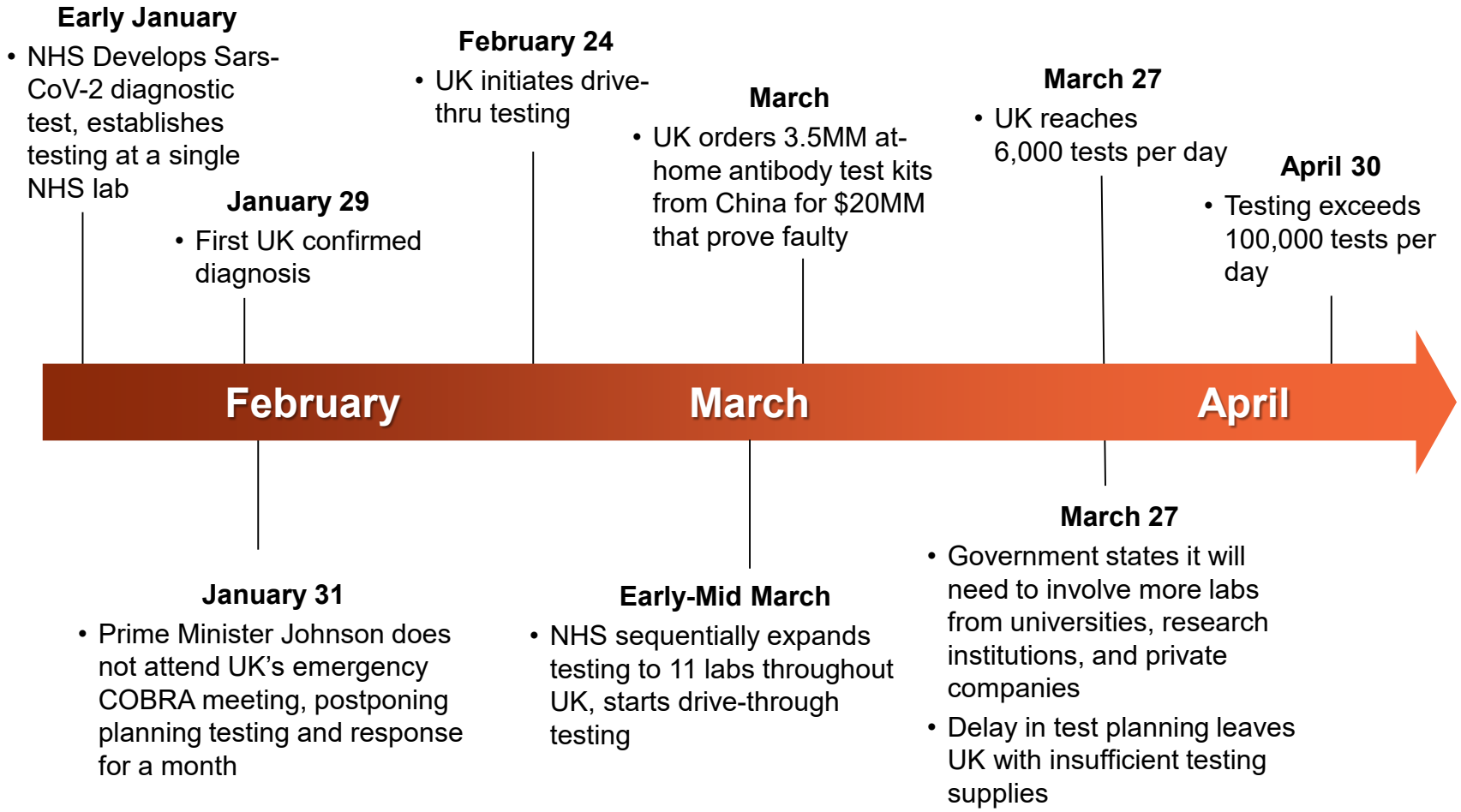
Note: CDC = Center for Disease Control (US); FDA = Food and Drug Administration; LDT = laboratory developed test; EUA = emergency use authorization; NIAID = National Institutes of Allergy and Infections Disease.

Source: Health Advances analysis, FDA, CDC.

What Was the Hold Up with SARS-CoV-2 Testing in the UK?

UK

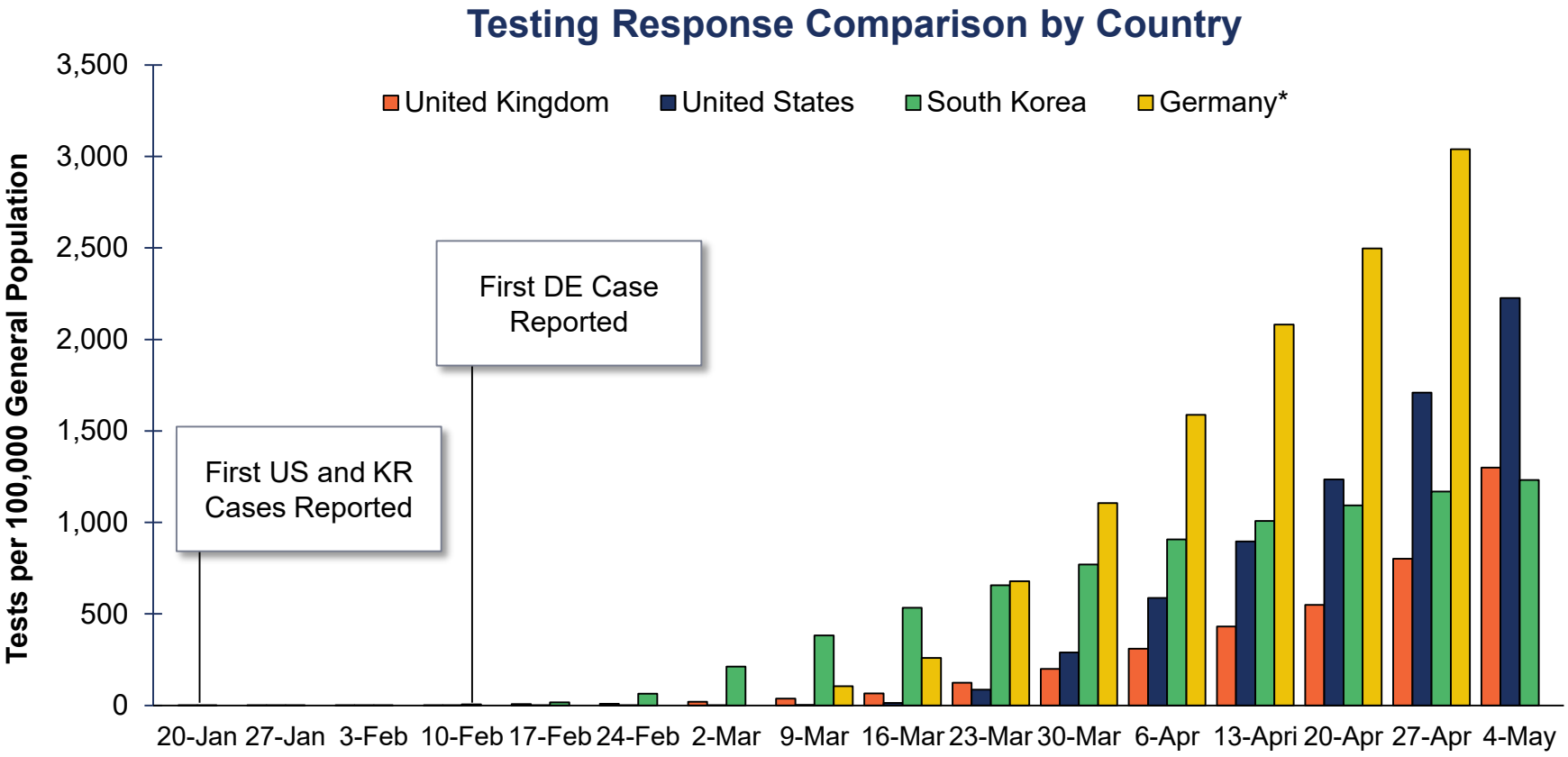
The UK's initial delay in testing response, despite early availability of a working test, from the UK National Health Service, has led to ongoing capacity issues.



Source: Health Advances analysis, BBC, Public Health England, The Atlantic, Financial Times.

Test Volume Timelines by Country

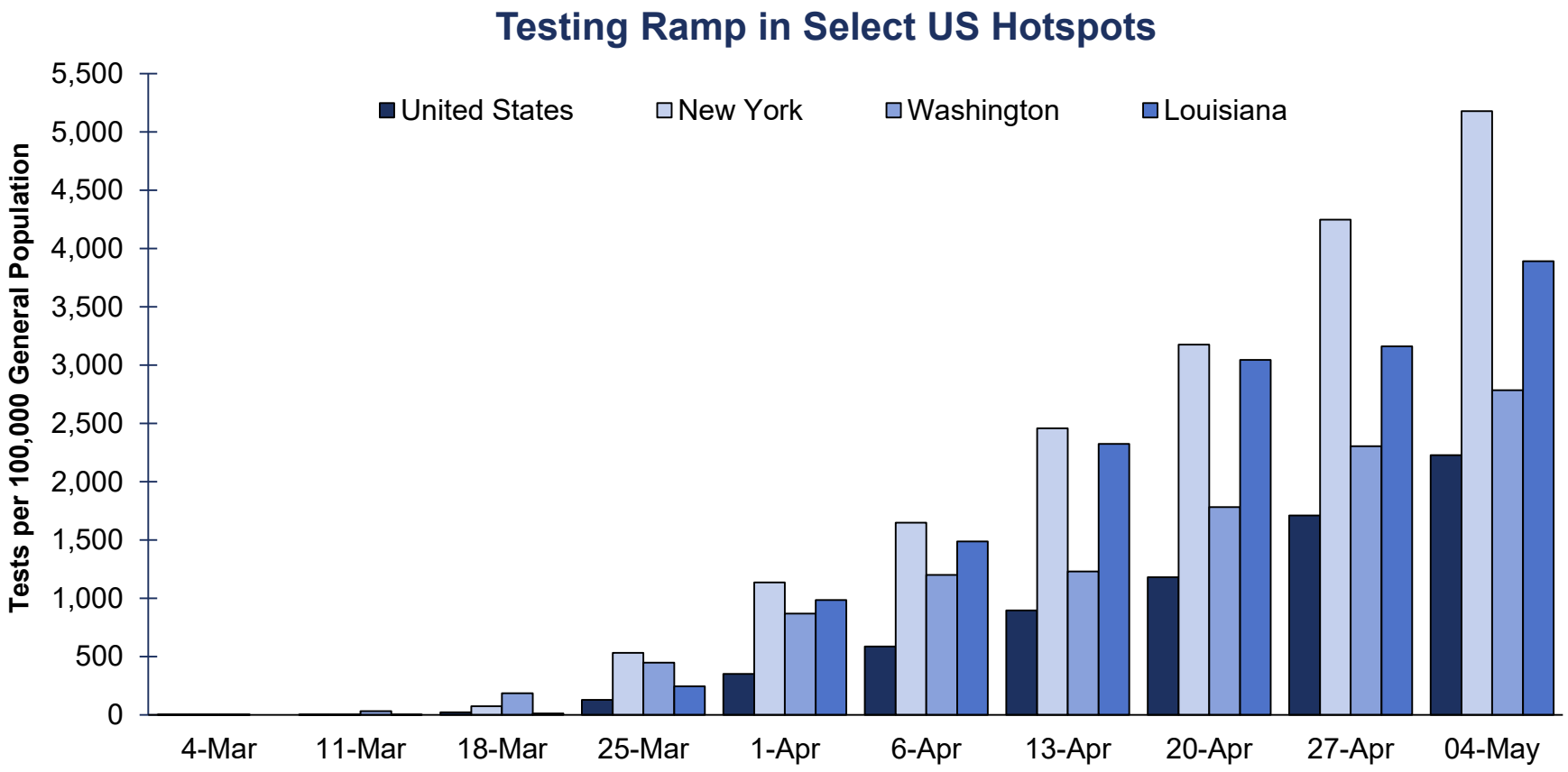
Both the German and South Korean responses worked quickly, while in the US, it took 8 weeks from the first case to ramp up testing and the UK is still lagging significantly.



Note: US and KR each had the first patient with confirmed SARS-CoV-2 on Jan 20, 2020. Data is up to date as of May 5, 2020.
* Germany data is reported as available.
Source: Health Advances analysis, COVID Tracking Project, CDC, country-specific government agencies.

Test Volumes in Select US States

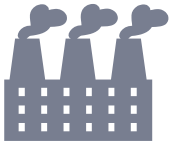
The US proved it can ramp up testing within hotspots (NY, WA, and LA) once the efforts were organized by local governments.



Source: Health Advances analysis, COVID Tracking Project, government agencies.

Key Learnings for Future Pandemic Responses

An early action plan from a centralized agency, combined with early manufacturing of test kits and early optimization of test logistics, are critical to a successful pandemic response.

Action Needed	Rationale
 **Early Action Plan from *Central* Government**	• South Korea and Germany both developed clear, early action plans outlining the various roles of government and private sectors • These plans were produced and distributed in mid to late January, a full month prior to a US and UK response
 **Engaging Commercial Manufacturers**	• KR immediately engaged commercial manufacturers to ramp up testing, while Germany initially used LDTs before authorizing commercial kits • The UK initially implemented testing and contact tracing effectively, but failed to ramp up testing capabilities to meet the rising demand • The US became inflexible in its regulatory policy delaying test launch and use
 **Closing the Testing Loop**	• Clear strategies for providing access to tests and contact tracing of confirmed positive patients is critical – KR performed contact tracing from the start, quenching the spread of the virus – Germany has recently (mid-March) implemented a contact tracing program and are even starting to use a mobile app (early-April)

Source: Health Advances analysis.

Agenda

- What do we know about markers of disease and recovery for SARS-CoV-2?
- What types and how much testing do we need now and in the future?
- Why was testing in the US slow to emerge?
- ***Why is it hard to get testing up and running? How is this different for molecular versus serology?***
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In Vitro Diagnostic Testing Approaches

In vitro diagnostic (IVD) testing utilizes components (reagents) that are combined with patient samples and run on instruments, which can be approached in several ways.

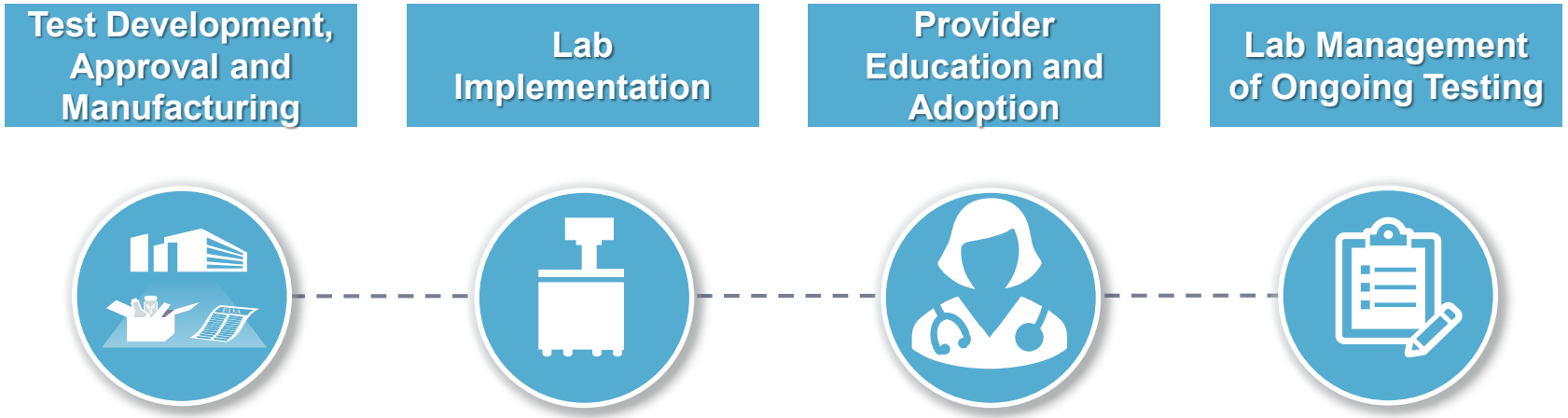
	Approach			Tools Needed		General Details *(not SARS-CoV-2 Specific)*
LAB	Laboratory-Developed Test (LDT)	 Individual lab acquires reagents, develops test protocol	+	 Lab uses open instrument* to run test		• Analogous to making a home-brew beer • Test cannot be sold to other labs
LAB	Lab Kit	 Manufacturer A provides test kits	+	 Manufacturer B provides open instrument*		• Similar to using different brands for your computer and software • Instruments are open (like a printer that could use ink from any company)
LAB	Lab Kit and Platform	 Manufacturer A provides reagent kits	+	 Manufacturer A provides closed instrument*		• Like Apple computer requires an Apple charger • Instruments are closed (similar to how printers are today that can only use ink from that company)
POC	Point-of-Care (POC)	 Manufacturer A provides test cartridge and instrument	or	 Test cartridge does not require instrument		• For use outside of lab • First option is similar to how diabetics measure their glucose • Second option is similar to pregnancy tests

* An open instrument allows any company's reagents to be used on the instrument, whereas a closed instrument restricts use to reagents made by the same manufacturer that makes the instrument.

Source: Health Advances analysis.

Steps and Stakeholders in Making ***Lab*** Testing Actually Available

Operationalizing ***lab*** testing for patients and clinicians is a multi-step process that includes manufacturers, government regulators, labs, hospitals and healthcare providers, and patients.



Source: Health Advances analysis.

Steps and Challenges in "Normal" Testing

Typically, a novel test launch faces challenges and requires a lengthy development cycle.

	Test Development, Approval and Manufacturing	Lab Implementation	Provider Education and Adoption	Lab Management of Ongoing Testing Logistics
				
				
Description	• Design and ensure test works • Obtain approval to sell/use test	• Acquiring test components • Validating test works in specific lab	• Educating providers on how and when to use the test • Setting up communication tools	• Ensuring steady supply of test components and patient samples
Key Challenges	• Developing a test requires critical components (e.g., reagents, etc.) • Proving a test works requires patient testing • Approval and manufacturing require high investment	• New tests often require learning new processes • Labs have multiple tests and processes to consider beyond performing test	• Understanding real-world test results can be complicated • Guidelines for how and when to use a test evolve over time	• Shortages of test components • Poor quality patient sample • Lab technicians to run tests

Note: EMR = electronic medical records.
Source: Health Advances analysis.

Challenges for SARS-CoV-2

For SARS-CoV-2, the goal of quickly ramping up has hit numerous roadblocks.

Challenges to Date for SARS-CoV-2

Test Development, Approval and Manufacturing	Lab Implementation	Provider Education and Adoption	Lab Management of Ongoing Testing Logistics
			
• Disease biology not yet well understood • Samples for validation not available • Insufficient supply of core reagents* needed to produce kits • Time to build manufacturing capacity • Regulatory rules in flux	• Samples for validation hard to find • Test quality differences unclear • Access to testing supplies lacking central coordination • Insufficient supply of materials	• Rapidly evolving testing paradigms; unclear which tests to use when • Which tests are available where is hard to keep track of • Interpretation of result challenging	• Lack of sample collection kits • Not enough trained staff (lab and sample collection)

* Example included extraction reagents for molecular viral RNA tests.

Source: Health Advances analysis.

Steps in Making ***POC*** Testing Available at Non-Lab Sites

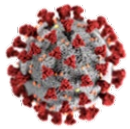
Similar steps are required to get POC testing up and running at non-lab sites, though it is less onerous than lab implementation given the simplicity of CLIA-waived POC tests.

	Test Development, Approval and Manufacturing	POC Testing Site Implementation	Provider Education and Adoption	Site Management of Ongoing Testing Logistics
				
Description	• Design and ensure test works • Obtain approval to sell/use test as POC • Manufacture tests	• Set up POC test at non-lab sites • Obtain necessary test kits	• Educate providers on how and when to use the test • Set up communication tools (EMR link if available)	• Ensure steady supply of test kits and patient samples
Key Challenges	• Requires critical components (e.g., reagents, etc.) • Must be simple enough for POC testing	• Provide limited training for HCPs (nurses, PAs) to operate test	• Can be difficult to train all clinicians	• Shortages of test kits • Poor patient sample quality

Source: Health Advances analysis.

POC Testing at Non-Lab Sites: SARS-CoV-2 Challenges

The largest hurdle for SARS-CoV-2 POC testing is gaining FDA approval for use at the POC as no clear rapid pathway for immunoassays has yet been provided.



SARS-CoV-2 Challenges

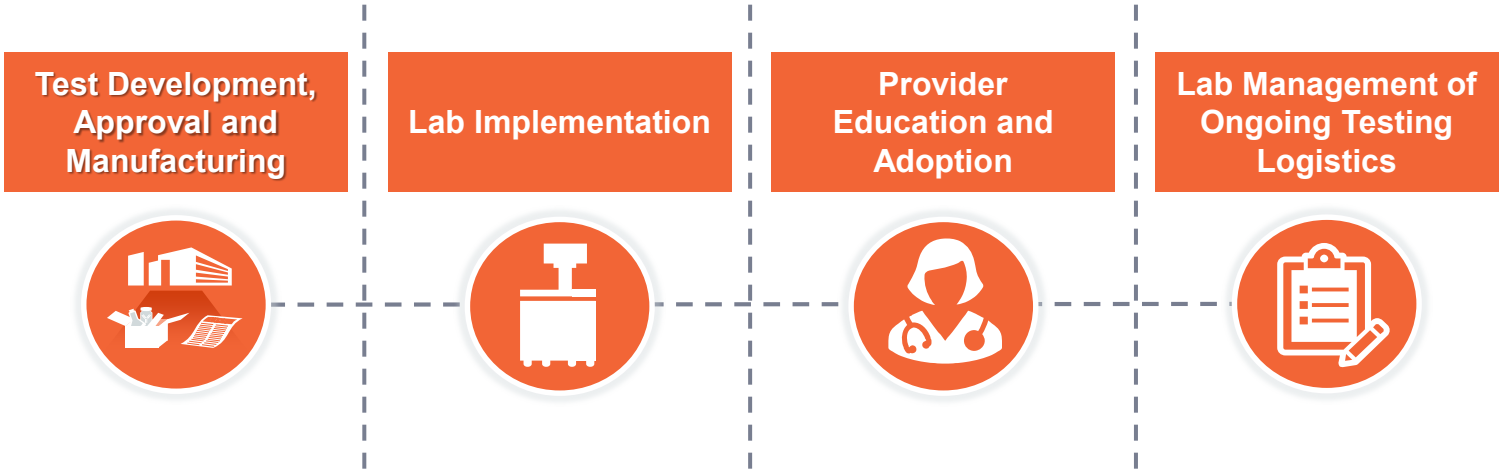
Test Development, Approval and Manufacturing	POC Testing Site Implementation	Provider Education and Adoption	Site Management of Ongoing Testing Logistics
• **Time crunch** to develop simple, highly accurate test in months rather than years • **Limited POC regulatory approval** (via EUA) – May need more rigorous studies than lab tests	• Must use **existing instruments*** – New instruments take weeks to months • **Limited supply** of sample collection kits and POC test kits • **Limited personnel** available to train clinicians	• **HCPs require education** on POC test use and availability • **Must prioritize patients** for POC vs. lab test	• **Poorly established sample collection/QC** given time pressure • **Limited POC throughput** (~1 sample/run) prevents high-volume testing

* Some tests do not require an instrument (are fully disposable) alleviating this challenge.

Source: Health Advances analysis.

Impact of Challenges and Possible Solutions SARS-CoV-2

The numerous challenges have lead to slow availability of tests, economic and logistical hardship that can only be addressed by improved testing solutions and coordination.



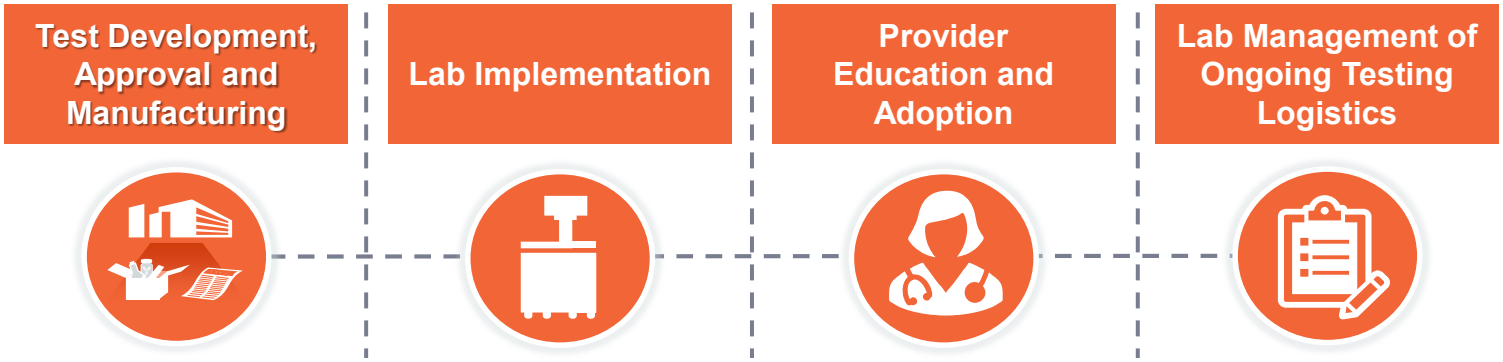
Impact of Challenges

- Test configurations (e.g. serology for IgG versus IgA or IgM) different between manufacturers and may not reflect disease progression
- Variability in test performance/quality
- Confusion among clinicians (where to send patients to get tested, which test to use, how to interpret results)
- Initial testing too restricted; reaching too few infected patients and their close contacts

Note: EMR = electronic medical records.
Source: Health Advances analysis.

Possible Solutions to Improve SARS-CoV-2 Testing and Containment

The numerous challenges have lead to slow availability of tests, economic and logistical hardship that can only be addressed by improved testing solutions and coordination.



Solutions

- Coordination of research studies to understand disease better
- Optimization of test format/configurations (e.g. total Ig versus individual, viral antigen tests by immunoassay for resource poor settings, panels with flu and/or RSV, self-testing)
- Massive ramp up of test manufacturing and lab capacity
- Use of different sample types (e.g. saliva) and sample collection methods (e.g. self-collection at home)
- Innovative approach to where and how testing is performed (e.g. workplace)
- Comparative clinical testing of different testing options to ensure the best tests are as widely available as possible

Source: Health Advances analysis.

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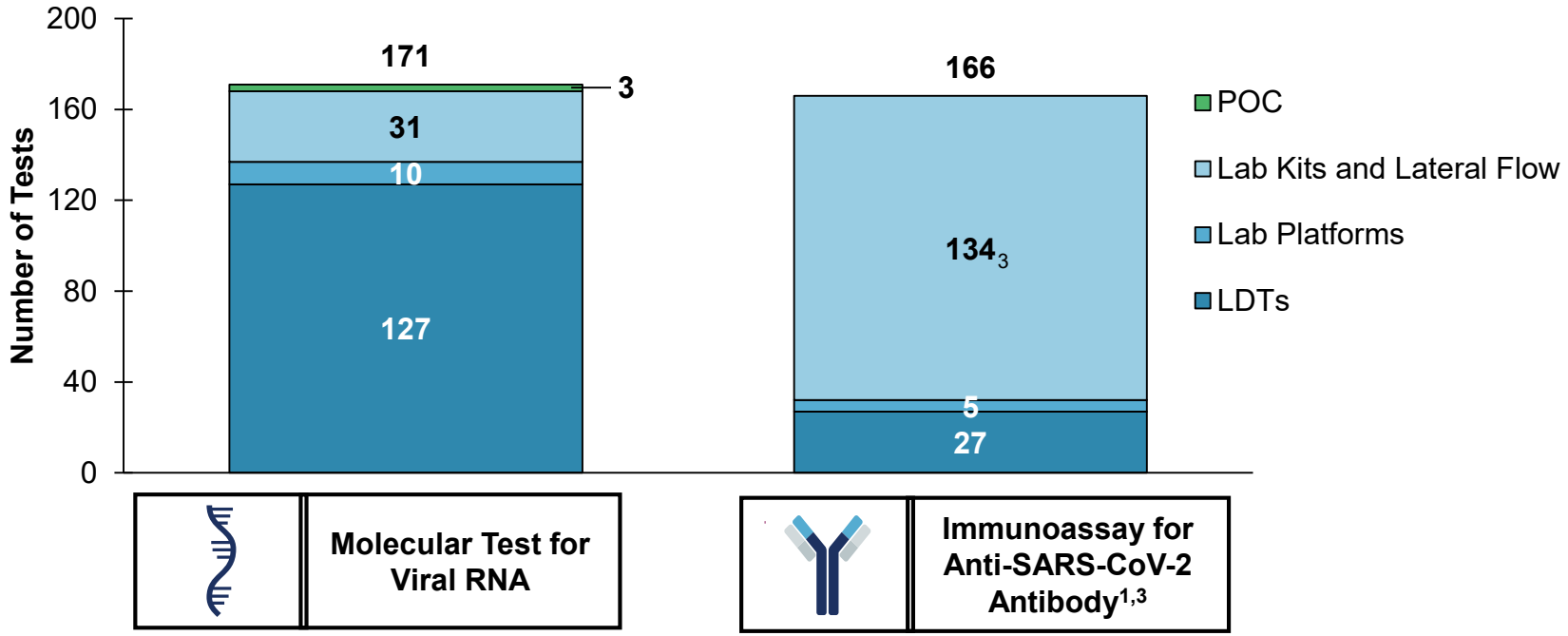
Status of SARS-CoV-2 Tests in the US

Updated 4/29/2020

To date, over 330 tests for SARS-CoV-2 have been developed for use in the US. Many more are in development.

Commercially Available SARS-CoV-2 Tests in the US[1]

EUA-Approved or EUA-Exempt or FDA-Notified (n=337)



[1] As of the date of this analysis, no serology-based tests have received an EUA for CLIA-waived testing (POC). All serology-based tests that have notified the FDA but not received an EUA may be used in high-complexity or moderate-complexity CLIA labs only. All serology-based tests for use in the US are anti-virus antibody-based tests. No viral antigen tests (for diagnosis) have received EUA or notified the FDA as of yet.

[3] As of May 4th, all of the serology tests that notified the FDA under "Policy D" will have 10 business days to submit EUA. During these 10 days they are still commercially available, but may not be after May 15th if manufacturers do not submit EUAs in time.

Note: EUA = Emergency Use Authorization. IA = Immunoassay.

Source: Health Advances analysis, FDA, GenomeWeb, FierceBiotech, company websites.

Representative US *LDTs* for Molecular RNA Diagnosis Testing

Updated 4/30/2020

LDTs from major commercial and academic labs, such as LabCorp and Rutgers respectively, are providing significant testing capacity.

Laboratory	LabCorp	Quest Diagnostics	BioReference Laboratories	RUCDR (Rutgers University)	Mayo Clinic	Avellino	ARUP Laboratories
LDT Testing Capacity per Month	1.8MM	1.5MM[1]	600,000[2]	300,000	210,000[3]	200,000[4]	150,000
Patient to Result TAT *(reported)*	1-2 days	< 2 days	1-3 days	1-2 days	1 day	1-2 days	1-4 days
EUA Status	EUA (3/16)	EUA (3/17)	No EUA; FDA notified under "Policy A"	EUA (4/10)	EUA (4/20)	EUA (3/25)	No EUA, FDA notified under "Policy A"
Real Time-PCR Platform *(open)*	ABI QS7 Flex[1]	ABI 7500[1]	Unknown	ABI QS5	Roche LightCycler 480	ABI 7500	Roche Cobas 6800/8800 or Hologic Panther

[1] Quest capacity also includes the Roche and Hologic tests, which are run on Cobas 6800/8800 and Panther platforms, respectively.
[2] Bioreference's capacity may include serology tests.
[3] Mayo capacity includes other commercially available tests.
[4] Avellino testing capacity is based on testing capacity projections.

Note: ABI = Applied Biosystems (Thermo Fisher Scientific). TAT = turnaround time, the time interval from when a specimen is received in a lab to when the result is available.
Source: Health Advances analysis, FDA, company websites.

Key US Lab *Kits* for Molecular RNA Diagnosis Testing

Updated 4/29/2020

More than 25 companies have an EUA for molecular test kits; IDT, Thermo, BGI, DiaCarta, and Quidel report the highest manufacturing capacity.

Company	BGI	ThermoFisher SCIENTIFIC	IDT INTEGRATED DNA TECHNOLOGIES / DANAHER	DIACARTA	QUIDEL
Stated Real-Time PCR Platform Compatibility[1]	Applied Biosystems (ABI) 7500 Real-Time PCR (Thermo Fisher Scientific)			• ABI QS5 • ABI 7500	• ABI 7500 • Roche LightCycler • Qiagen Roto-Gene Q
Manufacturing Capacity *(Tests/Month)*	60MM[2]	20MM[2]	20MM[3]	2MM[4]	1.5MM[2]

[1] While not stated in EUAs, most kits can be used with other real time PCR instruments.
[2] Thermo Fisher Scientific is producing 5MM tests/week as of 4/22/2020. BGI production has recently trebled to 2MM tests/day. Quidel plans to produce 50,000 tests/day by mid-April.
[3] As of March 16, IDT, the primer/probe kits used in the CDC testing protocol for SARS-CoV-2, estimated that it will manufacture 5MM tests/week.
[4] DiaCarta is estimating manufacturing capacity of 500,000 tests per week, and is planning to expand to even larger (4x) scale in the near future.

Source: Health Advances interviews and analysis, FDA, New York Times, company websites.

Key US *Lab Platforms* for Molecular RNA Diagnosis Testing

Updated 5/5/2020

Of the key lab platforms with molecular EUAs, Hologic and Abbott have the highest manufacturing capacity.

Company	Roche	HOLOGIC	HOLOGIC	BD	BIOFIRE BY BIOMÉRIEUX	Abbott
Platform	Cobas 6800/8800	Panther Fusion	Panther[2]	BD Max	FilmArray 2.0 and Torch	Abbott RealTime m2000
Assay TAT[1]	3-8 hours	<3 hours	3 hours	3 hours	50 minutes	5 hours
Tests per Hour	Up to 132	Up to 40	Up to 40	8	Up to 12	Up to 19
Platform Installed Base	~150 (US)	~150 (US)	1,000 (US)	Hundreds (US)	11,000 (WW)	200 (US)
Current Manufacturing Capacity per Month	1.6MM (WW)	600,000 (WW)	<4MM (WW)	200,000 (WW)	Not Stated	950,000 (WW)

[1] Does not account for sample transportation time.
[2] The Panther Aptima SARS-CoV-2 assay has not yet officially received EUA.
Note: Roche estimated total 3MM tests globally for the 6800/8800 systems. Abbott estimated 1MM test manufacturing capacity per week. Hologic estimates it will produce at least 1MM Aptima Sars-COV-2 assays per week for its Panther platform. Genmark and Abbott ID Now are two other major test sources that are not listed here.
Source: Health Advances interviews and analysis, FDA, company websites.

US *POC Platforms* for Molecular RNA Diagnosis Testing

Updated 5/5/2020

Three major diagnostic companies have received EUA for molecular SARS-CoV-2 POC diagnostics. Many more are in development but have not yet received EUA from the FDA.

Company	Abbott	Cepheid	mesabiotech
Platform	ID Now	Xpert Xpress	Accula
Authorized Setting	CLIA-Waived	CLIA-Waived	CLIA-Waived
TAT	5 minutes for a (+) 13 minutes for a (-)	45 minutes	30 minutes
Tests per Hour	3-6	Up to 4 (modular)	2
Platform Installed Base (US)	18,000	5,000	< 300
Manufacturing Capacity (Tests/Month)	1.5MM	Not Stated	40,000

Note: Abbott estimated its manufacturing capacity to be 50,000 tests/day, although has plans to scale up capacity to 2MM tests/month by June. Mesa estimated its capacity to be 10,000 tests/week.

Source: Health Advances interviews and analysis, FDA, company websites.

Molecular SARS-CoV-2 Test Performance Compared to Other ID Tests

The clinical sensitivity and specificity for SARS-CoV-2 tests remains unknown. However, other, *clinically-validated* molecular tests for respiratory illnesses have very high accuracy.

	Molecular SARS-CoV-2 *Coronavirus*		**Molecular Influenza A** *Flu*	**Molecular Streptococcus** *Strep Throat*	
	POC	**Lab Tests**	**POC and Lab Tests**	**POC**	**Lab Tests**
Clinical Sensitivity	Unknown	Unknown	**~96%**	**~97%**	**~100%**
Clinical Specificity	Unknown	Unknown	**~98%**	**~95%**	**~97%**
Limit of Detection	190 copies/mL	0.01 [$TCID_{50}$ / mL]	0.02 [$TCID_{50}$ / mL]	25 cells/mL	9 cells/mL
Impact (NPV/PPV)*	Unknown	Unknown	**NPV= ~98% PPV = ~88%**	**NPV= ~98% PPV = ~88%**	**NPV= ~100% PPV = ~86%**
Assay TAT	**5-45 minutes**	Hours	**5-30 minutes**	**5-20 minutes**	Hours

* NPV = negative predictive value, PPV = positive predictive value.

Note: The TCID50 (Median Tissue Culture Infectious Dose) signifies the concentration at which 50% of cells are infected when a test tube or well plate upon which cells have been cultured is inoculated with a diluted solution of viral fluid.

Source: Health Advances analysis, company data.

Performance Rating High Medium Low

Representative US *LDTs* for Serology Testing

Updated 5/5/2020

Several LDTs from major commercial and academic labs have begun to provide significant serological testing capacity. Only two have received formal EUAs.

Laboratory	Quest Diagnostics	LabCorp	Mayo Clinic	ARUP Laboratories	Lenco Diagnostic Laboratory	Health University of Minnesota	Emory Healthcare	Wadsworth Center NYSDOH	Mount Sinai
LDT Testing Capacity per Month	4MM	1.5MM	300,000	225,000[1]	60,000	30,000[2]	9,000[3]	"Thousands"	"Thousands"
Patient to Result TAT *(reported)*	1-2 days	3-5 days	1-3 days	1-3 days	Unknown	Unknown	Unknown	3-4 days	Unknown
EUA Status	No EUA; FDA notified under "Policy D"	No EUA; FDA notified under "Policy D"	No EUA; FDA notified under "Policy D"	No EUA; FDA notified under "Policy D"	No EUA; FDA notified under "Policy D"	No EUA; FDA notified under "Policy D"	No EUA; FDA notified under "Policy D"	Received EUA (4/30)	Received EUA (4/15)
Test Type *(Instruments Used)*	ELISA *(Unknown)*	ELISA *(Unknown)*	ELISA *(Unknown)*	ELISA *(Unknown)*	CL IA *(Diazyme DZ-Lite 3000)*	ELISA *(Unknown)*	Unknown	Microsphere IA *(Luminex FlexMap)*	ELISA *(Thermo Scientific Immulon)*

[1] ARUP will soon be able to perform 7,500 testing capacity/day but plans to increase to 30,000 tests/day in near future.
[2] U Minnesota is planning to ramp up to 15,000 tests/day in next 3-4 weeks in conjunction with Mayo Clinic, up from ~1,000 tests/day currently.
[3] Emory is currently testing 300 people/day, but hopes to reach goal of 5,000 antibody tests/day by mid-June.

Note: IA = immunoassay, CL = chemiluminescence, ELISA = enzyme-linked immunosorbent assay, TAT = turnaround time, the time interval from when a specimen is received in a lab to when the result is available.

Source: Health Advances analysis, FDA, company websites.

US "Policy C" Serology Lab Kits and Platforms (1 of 2)

Updated 5/5/2020

Many of the established diagnostics companies have achieved EUA for SARS CoV-2 serology tests and boast large manufacturing capacity.

Company	Abbott	Roche	Ortho Clinical Diagnostics		DiaSorin	BIO-RAD
Platforms	ARCHITECT i1000SR and i2000SR	Cobas e (e411, e601/602, e801)	• VITROS XT7600/3600/5600 • VITROS Eci/ECiQ		Liaison XL	Manual or on automated ELISAs, such as EVOLIS
Antibody Detection	IgG	Antibodies against Sars CoV-2 including IgG	Total antibody	IgG	IgG	Total antibody
TAT	29 minutes	18 minutes	50 minutes		35 minutes	~2 hours
Tests per Hour	200	300	150		170	300[4]
EUA Received	4/26/2020	5/2/2020	4/14/2020	4/24/2020	4/24/2020	4/29/2020
Platform Installed Base	2,000 (US)	40,000 (WW)	>1,000 (US)		600 (US)	Not applicable
Manufacturing Capacity per Month	4MM (US)[1]	5MM (WW)[2]	"Several Million" (WW)		~1MM (WW)[3]	Not Stated

[1] Abbott announced it shipped 4MM tests in April, and is on track to ramp up production to 20MM tests per month by June.
[2] Roche plans to ramp up manufacturing capacity to high double-digit millions of tests per month by end of June.
[3] DiaSorin plans to manufacture several millions of tests over the next several months.
[4] Biorad tests per hour is based on use of EVOLIS system

Source: Health Advances analysis, FDA, company websites.

US “Policy C” Serology Lab Kits and Platforms (2 of 2)

Updated 5/5/2020

A handful of smaller serology test manufacturers have also received EUAs, largely lateral flow devices and ELISAs.

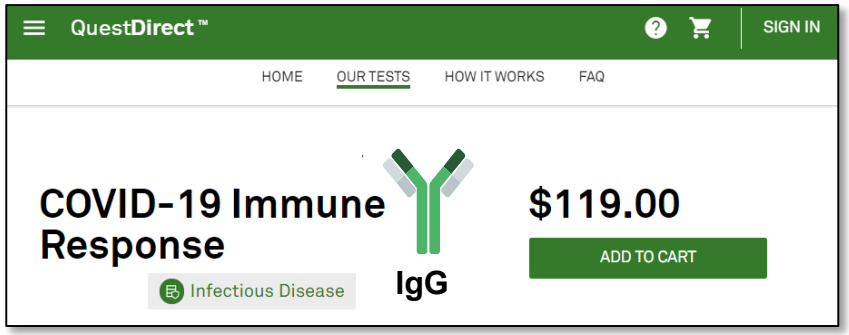
Company	EUROIMMUN a PerkinElmer company	CHEMBIO DIAGNOSTIC SYSTEMS, INC.	Cellex™	Autobio
Platforms	Tecan Sunrise, Infinite 50, EUROIMMUN Analyzer I/I-2P, EUROLabWorkstation (not required)	DPP MicroReader	N/A (Lateral Flow)	N/A (Lateral Flow)
Antibody Detection	IgG	IgG and IgM	IgG and IgM	IgG and IgM
TAT	3 ½ hours	15 minutes	15-20 minutes	15-20 minutes
Tests per Hour	Up to 198	4	4	4
EUA Received	5/4/2020	4/14/2020	4/1/2020	4/24/2020
Platform Installed Base	N/A (ELISA)	Unknown	N/A (lateral flow)	N/A (lateral flow)
Manufacturing Capacity per Month	“Millions”	Not Stated	Not Stated	Not Stated

Source: Health Advances analysis, FDA, company websites.

First Consumer-Initiated Antibody Test Available

On April 28, Quest announced the first consumer-initiated US antibody test. The service uses antibody tests from two well-known manufacturers.

Quest Diagnostics™



- Launched April 28
- Patients must meet guidelines (no symptoms, >14 days post exposure/symptom initiation)
- Blood samples collected at Quest sites
- Detects IgG antibody with one of two tests
  - SARS-CoV-2 IgG Assay (Policy C) from Abbott
    - Analytical specificity of 99%
    - Analytical sensitivity of >95% (≥14 days post-symptom onset only)
  - Anti-SARS-CoV-2 ELISA IgG Test (Policy C) from EUROIMMUN
    - Analytical specificity of 100%
    - Analytical sensitivity of 90%

Note: The Abbott IgG assay's analytical sensitivity ranges from 0% - 86% for samples tests of patients <14 days post-symptom onset.
Source: Health Advances analysis, FDA, Quest Diagnostics, PR Newswire, Lassauniere 2020 MedRxIV, Kruttgen 2020 J Clin Virology, company websites.

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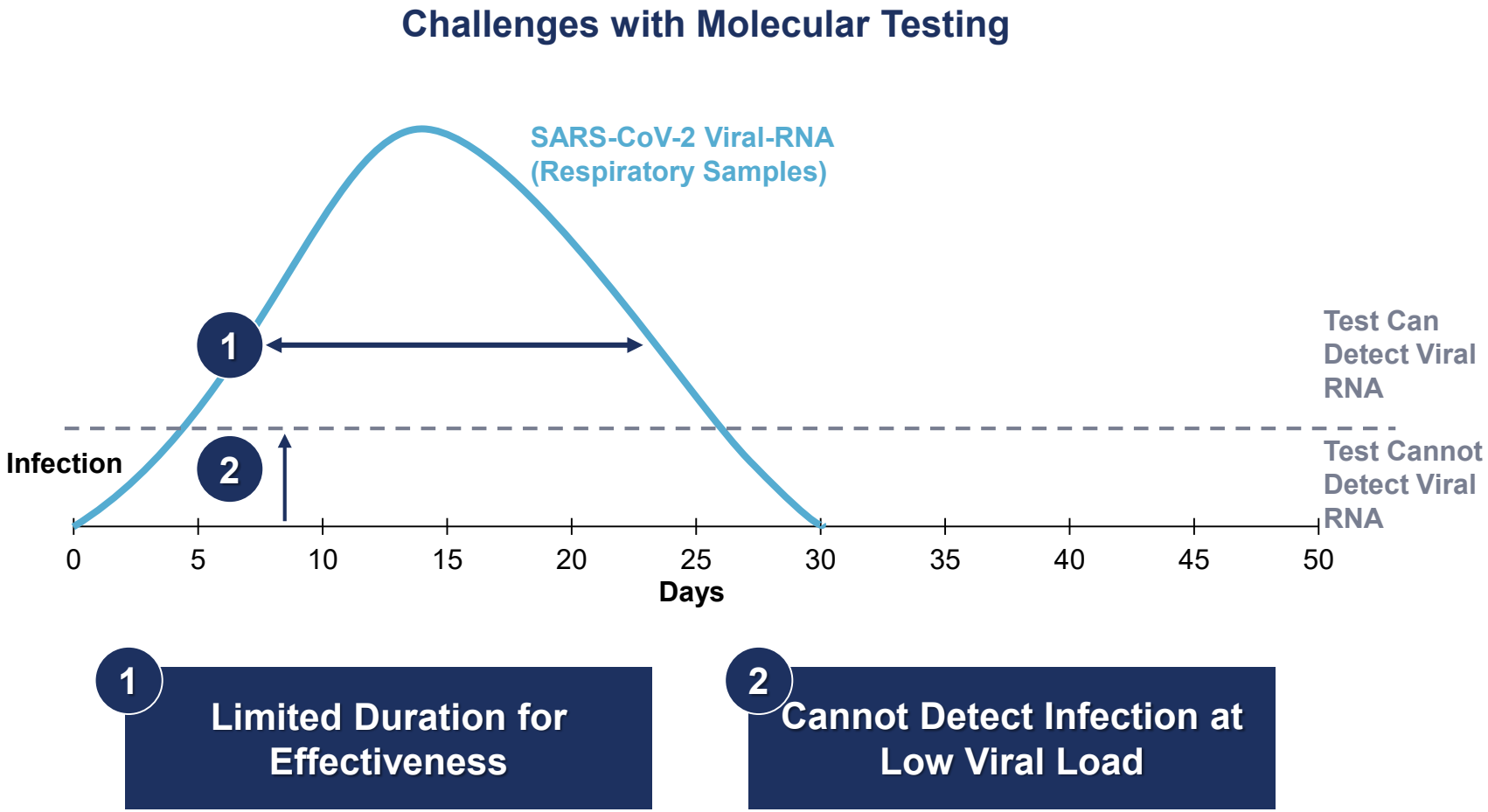
Challenges with Molecular Testing

Molecular tests face two challenges, both of which may be clinically meaningful: ability to detect viral RNA for only a short window and inability to detect infection at low viral loads.



Source: Health Advances analysis.

Challenges with Serology Testing

Serology tests face many more challenges. Most importantly, poor test performance has created major validation and result interpretation challenges.

Poor Performance
(False Positives and Negatives)

Need for Validation Studies

Confusion on Result Interpretation

- Many currently available serology tests report many false positive or false negative results
- Caused in part by rushed launch of tests with minimal analytic validation prior to commercialization

- Serology tests trade off sensitivity and specificity, so different tests do not give same results
- Lab cannot easily determine which tests to use
- Clinicians are confused how to interpret results
  - Some clinicians do not understand that a positive antibody result does not indicate active infection
  - Some clinicians falsely assume that positive result indicates immunity

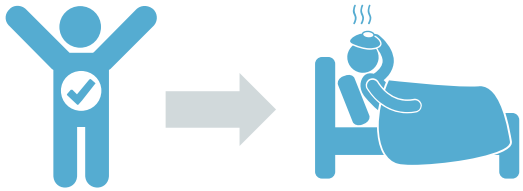
Source: Health Advances analysis, FDA, company websites.

Serology Performance Challenges: Impact of False Results

Poorly performing assays produce false positive and false negative results, both of which are very detrimental to our efforts to carefully lift social distancing restrictions.

False Positive

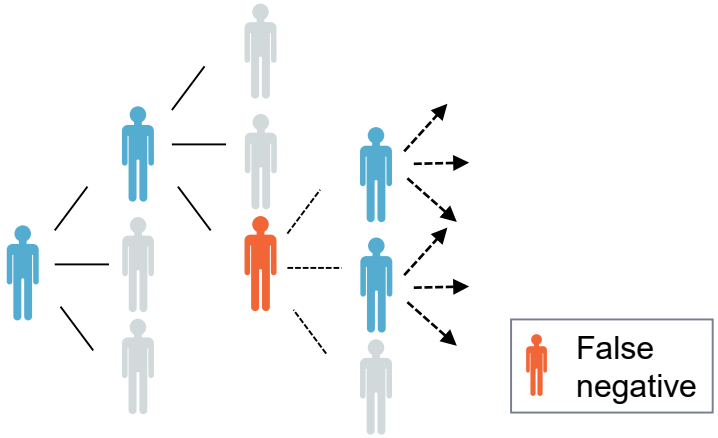
Expose People without Potential Immunity to Infection



- Crucial use case for serology tests is to identify those who may have been exposed and have potential immunity
- A false positive result would falsely suggest that someone is able to return to work, subjecting that person to infection risk and driving resurgence

False Negative

Lose the Trail of Track-and-Trace



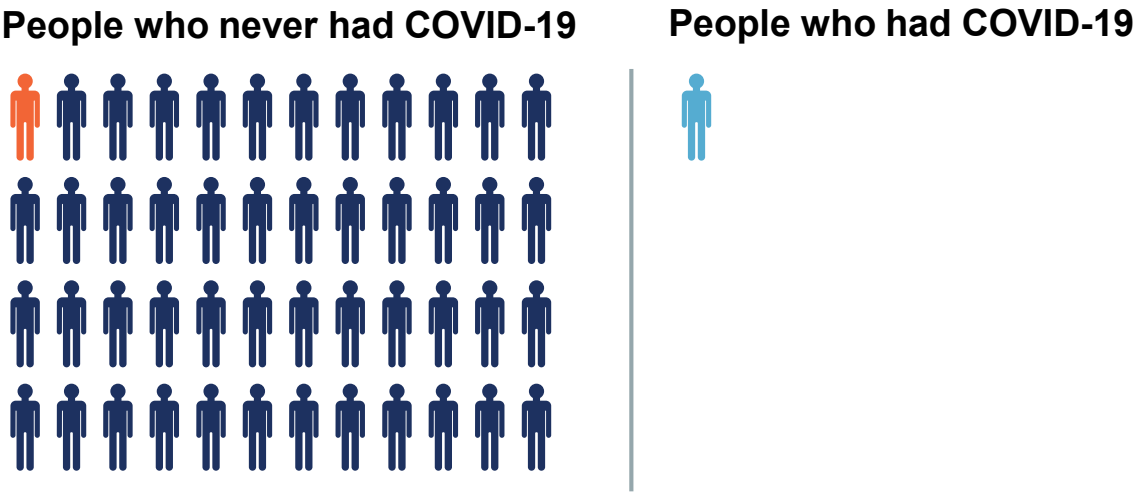
- In tandem with testing, contact tracing is critical for us to manage the pandemic after shelter-in-place is lifted
- False negative results disrupt the ability of track-and-trace to effectively monitor infection outbreaks

Source: Health Advances analysis.

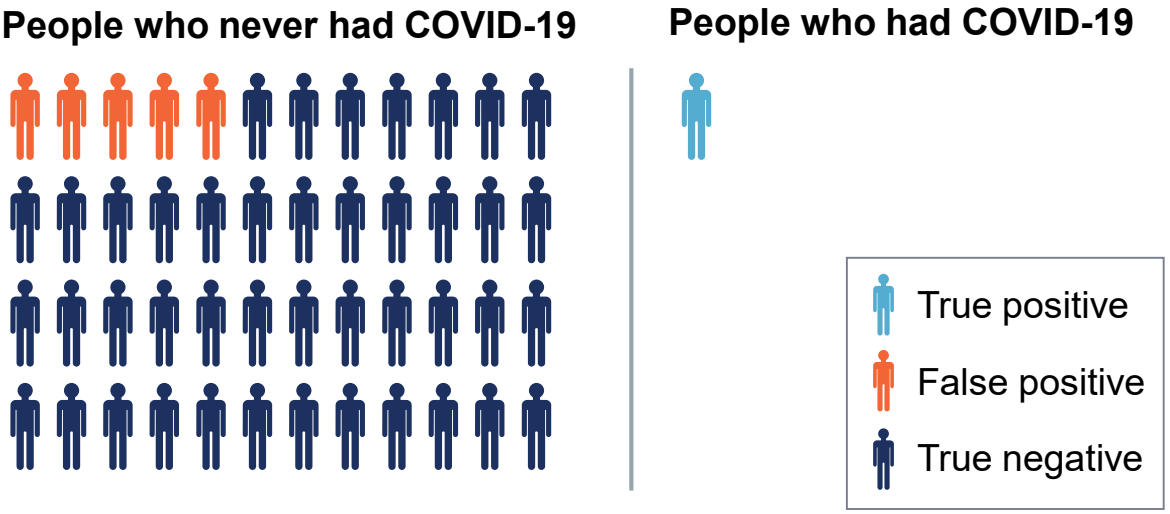
Serology Performance Challenges: Degree of Impact

Small differences in a test's specificity can make a huge difference for the number of false positive results. The same is true for a test's sensitivity and false negative results.

- Assume ~2% of population had SARS-CoV-19
- A test that is 100% sensitive and 98% specific will have as many false positives as true positives



- Assume ~2% of population had SARS-CoV-19
- A test that is 100% sensitive and 90% specific will have more false positives than true positive



Source: Health Advances analysis.

Serology Performance Challenges: How to Solve the Problem?

Validation and comparative studies will highlight performance variation among serology tests, but conducting robust studies quickly is challenging.

Rigorous development and validation assays using:

- Samples from SARS-CoV-2 patients, including:
  - Different stages post-symptom onset (days)
  - Different levels of infection severity
  - Different molecular subtypes of SARS-CoV-2
- Samples from patients never exposed to SARS-CoV-2 (from prior to outbreak), with subsets to represent:
  - Healthy patients
  - Patients infected with other respiratory viruses that could potentially cross-react to anti-SARS-CoV-2 antibodies, including other coronaviruses
- IgG vs. Total IgG/IgM tests, and with consideration to other technical differences between individual tests

But near-term challenges remain…

- Early studies have made progress*, but remain limited in scope
  - Limited number of samples tested in nearly all studies
  - Evaluated samples skewed towards hospitalized, seriously ill patients
  - Primarily done with manual lateral flow tests, not instrument-based tests
  - Prospective trials with blinded samples not conducted
- Many additional studies planned, but timeline for completion is unknown
  - FDA is currently forming task force to validate accuracy of samples
  - FIND working in collaboration with WHO and others to independently evaluate tests

* In particular, the early serologic test evaluation efforts from Whitman 2020 et al. (UCSF/UC Berkeley), Lassauniere 2020 et al. (Denmark), and Crook 2020 et al. (UK) are commendable.

Note: FIND = Foundation for Innovative New Diagnostics.

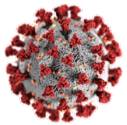
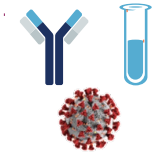
Source: Health Advances analysis, Whitman 2020, Lassauniere 2020, Crook 2020, GenomeWeb, Johns Hopkins 2020 National Strategy for Serology Testing.

Agenda

- What do we know about markers of disease and recovery for SARS-CoV-2?
- What types and how much testing do we need now and in the future?
- Why was testing in the US slow to emerge?
- Why is it hard to get testing up and running? How is this different for molecular versus serology?
- What tests are available for SARS-CoV-2 testing in the US today?
- What are the challenges and outlook for the available tests?
- ***Appendix***

What Tests Measure

Diagnosis requires detecting the virus in the body, while screening for exposure and immunity status requires detection of anti-virus antibodies.

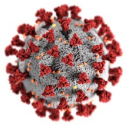
Clinical Reason for Testing		What the Test Measures
Diagnosis	 SARS-CoV-2 Virus	• To confirm[1] an ongoing/current infection, the virus itself must be detected in the body
Prognosis	 Combination of Virus, Antibody, and Health Tests	• To date, this is unclear • Likely a combination of viral load, anti-virus immune response, and other parameters (e.g., # of blood cells)
Exposure Screening/ Infection History **Immunity Status**	 Anti-virus Antibodies[2]	• To determine prior infection or likelihood to be immune, a test looks for the presence of anti-virus antibodies produced by the immune system • The presence of anti-virus antibodies does not definitively indicate a person is immune

[1] Anti-virus antibody testing can also help with diagnosis, but should not be used alone for this purpose.
[2] Antibodies are a protein the body's immune system produces in response to an infection. Antibodies identify the infection as foreign and direct other parts of the immune system to attack and neutralize/destroy the infection.

Source: Health Advances analysis, Lab Tests Online.

Types of Tests That Measure SARS-CoV-2 Virus and Immune Response

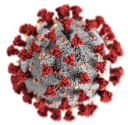
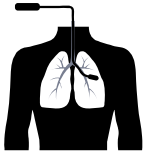
Multiple measurement types, called molecular tests and immunoassays (IA), can be used to detect virus. Immune system response requires IA to detect anti-virus antibodies.

What the Test is Measuring		Type of Test
Diagnosis	 Virus	Molecular Test for Viral RNA[1]
		Immunoassay for Viral Proteins[2]
Exposure Screening/ Infection History	 Anti-Virus Antibodies	Immunoassays for Anti-SARS-CoV-2 Antibody
Immunity Status		

[1] RNA stands for ribonucleic acid. Coronaviruses RNA is the genetic information that enables the virus to replicate.
[2] Viral proteins refers to any protein part of the virus itself that can be detected via an immunoassay.
Source: Health Advances analysis, Lab Tests Online.

Sample Types for SARS-CoV-2 Testing

Diagnostic testing to detect the actual virus requires samples from the respiratory tract. Anti-virus antibodies require a blood sample from your finger or vein.

Clinical Reason	What Needs to Be Detected by the Test	Relevant Sample Types				
Diagnosis	 **Virus** (either RNA or viral particle protein)	 **Saliva or Sputum**	 **Throat Swab**	 **Nasal Swab**	 **Nasopharyngeal (NP) Swab**	 **Bronchial Lavage**
		• Easier to collect • Higher chance of missing virus due to less virus content in sample			• Intrusive • Takes training to collect well • High virus amount; best sample type	• Complex • Can only be performed in hospital
Exposure Screening/ Infection History	 **Anti-Virus Antibodies**	 **Finger Stick**			 **Whole Blood, Serum or Plasma**	
		• Simpler to collect, but more difficult to quantify antibody amounts			• Potentially more painful for some, but provides enough sample to quantify antibody amounts	

Source: Health Advances analysis, CDC.

Summary of SARS-CoV-2/COVID-19 Testing

Updated 5/04/2020

SARS-CoV-2 testing is performed for a variety of clinical purposes. Today testing is focused on diagnosis via the most widely available method, which is molecular viral RNA.

Clinical Purposes of SARS-CoV-2 Testing			Relevant Test Type
Patients with Suspected Active Infection	Diagnosis	• Confirm the presence of SARS-CoV-2 in a symptomatic (or asymptomatic) patients	Molecular Test for Viral RNA; Immunoassay for Viral Proteins
	Prognosis	• Assessment of potential COVID-19 disease severity/disease progression	Combination of Virus, Immunity and Health Tests
Exposed Individuals and/or Those with Known Previous Infection	Exposure Screening/ Infection History	• Determine if a patient was previously infected with SARS-CoV-2 (whether or not they had symptoms)	Immunoassay for Anti-SARS-CoV-2 Antibody
	Immunity Status	• Predict the ability of a previously infected patient to resist future infection based on presence of anti-SARS-CoV-2 antibodies	Immunoassay for Anti-SARS-CoV-2 Antibody

■ Widespread Use Today □ Limited Use Today

Source: Health Advances analysis.

US, UK, KR, and DE Testing Response

The US and UK both delayed widespread testing until late March. In contrast, within a week of infection South Korea and Germany were rapidly establishing national testing.

Differences in Government Responses

US

- In the US, early testing relied on CDC
  - CDC test had technical problems
  - FDA would not allow labs to use other tests
- Eventually the FDA gave new guidance on EUA to allow other tests
  - Feb 29: High complexity CLIA labs could begin using LDTs after validation but before EUA review
  - Mar 16: Commercial manufacturers could distribute test kits after validation but before EUA review and states could handle LDTs within their borders

United Kingdom

- In mid-Jan, the NHS developed a test and deployed it at a single lab
- Widespread testing was not initially pursued
- Other NHS labs were sequentially added as infection spread over Feb.-Mar.
- Engagement with commercial partners finally initiated late March
- Purchase of serological tests that turned out to be inaccurate complicated testing roll out further

South Korea

- After a 2015 MERS outbreak, South Korea implemented policy changes to ensure proper testing
  - All testing paid for by government
  - Coordinated response and data submission
- South Korea engaged commercial partners on Jan 27 to enable quick authorization and manufacturing of tests
- Broad testing of population implemented immediately

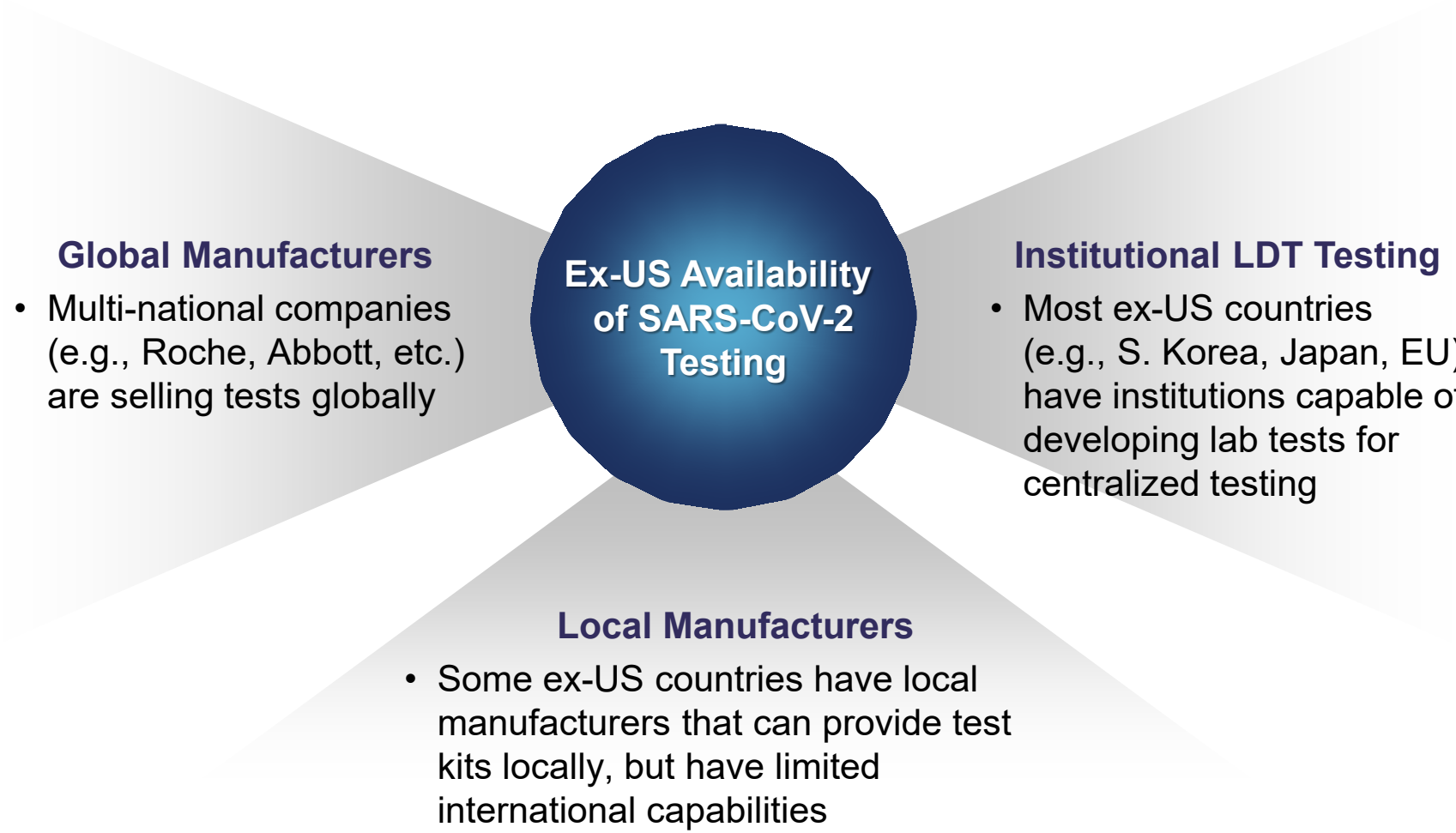
Germany

- In mid-Jan, German labs developed tests and built up stock in preparation to quickly test and isolate large swaths of the population
- Germany's dedicated virology labs and high experience with LDTs enabled immediate and widespread testing
- Germany has implemented innovative testing strategies (e.g., block tests) and explicitly attempted to replicate strategies from Korea and Singapore

Source: Health Advances analysis, FDA, CDC, government agencies, news reports.

Ex-US Availability of SARS-CoV-2 Tests

In addition to tests from the same multi-national manufacturers as the US (e.g., Abbott, Roche, etc.), ex-US countries have also relied on local labs and manufacturers.



Source: Health Advances analysis.

Sensitivity and Specificity

Sensitivity measures a test's ability to correctly identify patients with disease, and specificity measures the ability to correctly identify patients without disease.

		Actual Patient Status	
		Has Disease	Does not have Disease
Test Outcome	Positive Test	True Positive (Tp)	False Positive (Fp)
	Negative Test	False Negative (Fn)	True Negative (Tn)
		Sensitivity	Specificity

Sensitivity

"I believe my patient has the disease. What is the chance that the test will indicate the patient is positive for the disease?"

- The likelihood a test will correctly identify a positive patient as positive
- 100% means the test always calls a patient **with** infection as positive, and never negative
  - If a test is given 10 positive samples and it calls 7 positive and 3 negative (i.e. false negatives) the sensitivity is 70% (Tp/(Tp + Fn))
- SNOUT: good SeNsitivity rules OUT a disease

Specificity

"I believe my patient doesn't have the disease. What is the chance that the test will show my patient is negative for the disease?"

- The likelihood a test will correctly identify a negative patient as negative
- 100% specificity means the test always calls a patient **without** infection as negative, and never as positive
  - If a test is given 10 negative samples and it calls 8 negative and 2 positive (i.e. false positives) the specificity is 80% Tn/(Tn + Fp)
- SPIN: good sPecificity rules IN a disease

Source: Health Advances interviews and analysis, Johns Hopkins Bloomberg School of Public Health, Journal of Family Practice.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

PPV and NPV combine sensitivity and specificity, providing a useful view of test performance in predicting if a “positive means positive” and “negative means negative”.

		Actual Patient Status		
		Has COVID-19	Does not have COVID-19	
Test Outcome	Positive Test	True Positive	False Positive	Positive Predictive Value
	Negative Test	False Negative	True Negative	Negative Predictive Value
		Sensitivity	Specificity	

Positive Predictive Value

“I just got a positive test result back on my patient. What is the chance that my patient actually has the disease?”

- The likelihood a patient is positive, if the test is positive
- 100% PPV means the patient is guaranteed to have the disease if the test reads positive (never commits a false positive)
  - If a patient receives a positive result from a test with a 50% PPV, there is a 50% chance the patient has the disease (Tp/(Tp+ Fp)
- IMPORTANT: The more people in the group being tested that are positive, the higher PPV!

Negative Predictive Value

“I just got a negative test result back on my patient. What is the chance that my patient actually doesn’t have the disease?”

- The likelihood a patient is (-) if the test is (-)
- 100% NPV means the patient is guaranteed to be free of disease if the test reads negative (never commits a false negative)
  - If a patient receives a negative result from a test with a 90% NPV, there is a 90% chance the patient does not have the disease (Tn/(Tn+ Fn)
- IMPORTANT: The more people in the group being tested that are positive, the lower the NPV!

Source: Health Advances interviews and analysis, Johns Hopkins Bloomberg School of Public Health, Journal of Family Practice.

More Details: PPV/NPV and Sensitivity/Specificity Relationship

Sensitivity, specificity, NPV and PPV all have value though the questions clinicians ask are more reliably answered by understanding NPV and PPV.

PPV/NPV vs. sensitivity/specificity

- Sensitivity and Specificity are fixed characteristics of a test
- PPV/NPV vary based on the prevalence of the condition in the population being tested
  - Prevalence is the % of people in the population that actually have disease
- As the prevalence decreases there is a natural increase in NPV at the expense of PPV
- As prevalence increases, the PPV will increase, NPV will decrease and more patients will be called positive
- If another test has higher sensitivity and/or lower specificity more patients will test positive (NPV will go up and PPV down)
- Example:
  - A coin flip with 50% sens/spec can still have high NPV if the condition is rare.
  - If the prevalence of the disease is 1 in 1000, even a negative result from a coin flip is accurate more than 99% of the time (NPV).

- PPV and NPV can also be calculated as follows
  - PPV = sens X prev / (sens x prev + (1-spec) x (1- prev)
  - NPV = spec X (1-prevalence) / (spec X (1-prev) + (1-sens) X prev)

Prevalence	5%	15%	25%
Example 1 - 90% Sensitivity, 90% Specificity			
NPV	99%	98%	96%
PPV	32%	61%	75%
Percent tested that are called positive	14%	22%	30%
Example 2 - 90% Sensitivity, 70% Specificity			
NPV	99%	97%	96%
PPV	14%	35%	50%
Percent tested that are called positive	33%	39%	45%
Example 3 – 70% Sensitivity , 90% Specificity			
NPV	98%	94%	90%
PPV	27%	55%	70%
Percent tested that are called positive	13%	19%	25%

Source: Health Advances interviews and analysis, Johns Hopkins Bloomberg School of Public Health, https://www.medcalc.org/calc/diagnostic_test.p%hp

Lab Test Development

First, manufacturers (or labs) must develop and validate a test to obtain regulatory clearance/approval to sell or use the test.

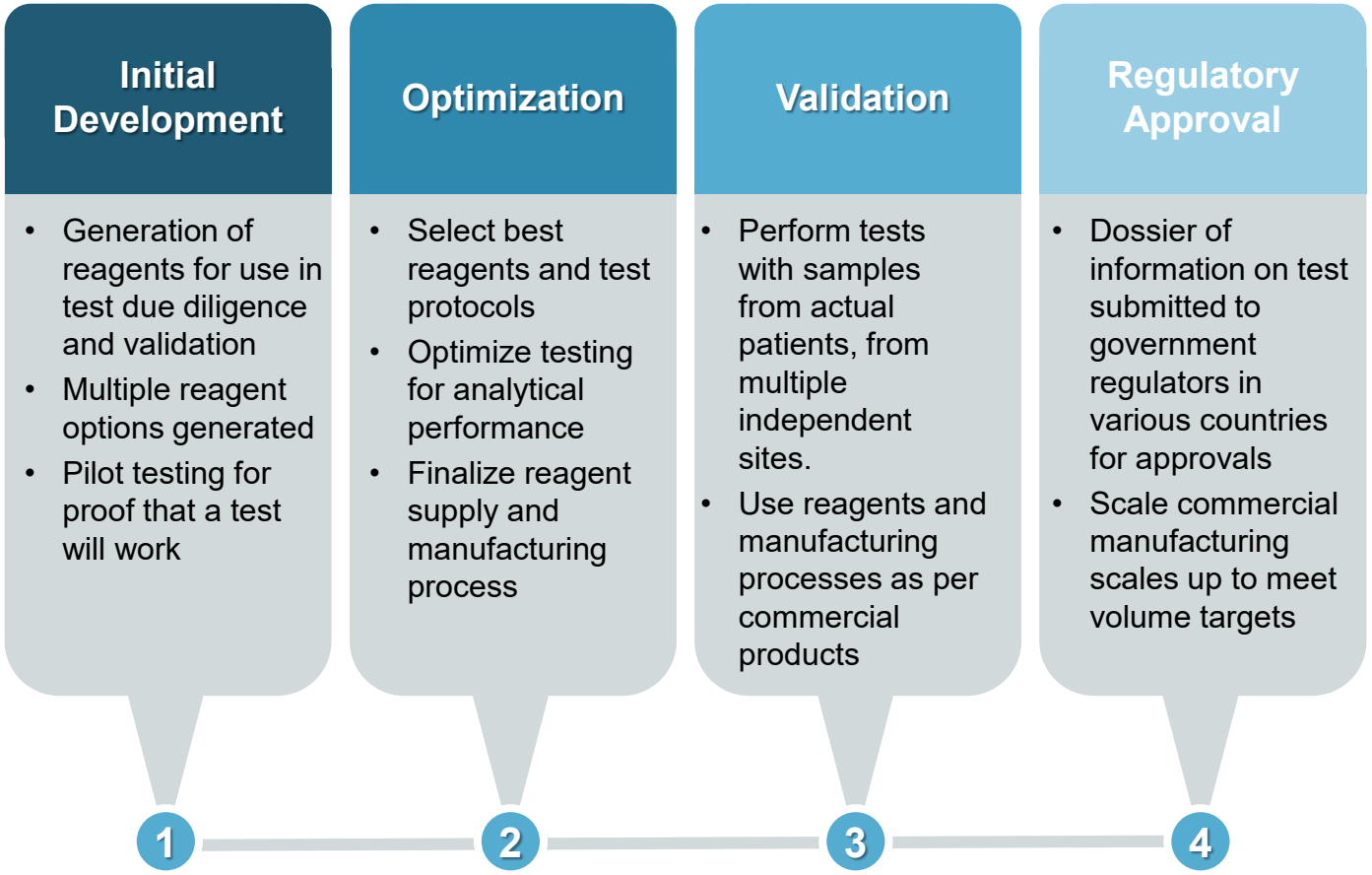
	Test Development, Approval and Manufacturing	Lab Implementation	Provider Education and Adoption	Lab Management of Ongoing Testing Logistics
				
Description	• Design and ensure test works • Obtain approval to sell/use test			
Key Challenges	• Developing a test requires critical components (e.g., reagents, etc.) • Proving a test works requires patient testing • Approval and manufacturing require high investment			

Source: Health Advances analysis.

Steps in Test Development and Regulatory Approval

A typical test development process involves an extensive program designed to ensure that the test provides accurate results and that the system is robust and reliable.

Stages of Test Development and Regulatory Approval



Source: Health Advances interviews and analysis.

Timeline of Test Development and Regulatory Approval

Test development typically requires several years. Immunoassays, like anti-SARS-CoV-2 antibody tests, require more time than molecular tests.

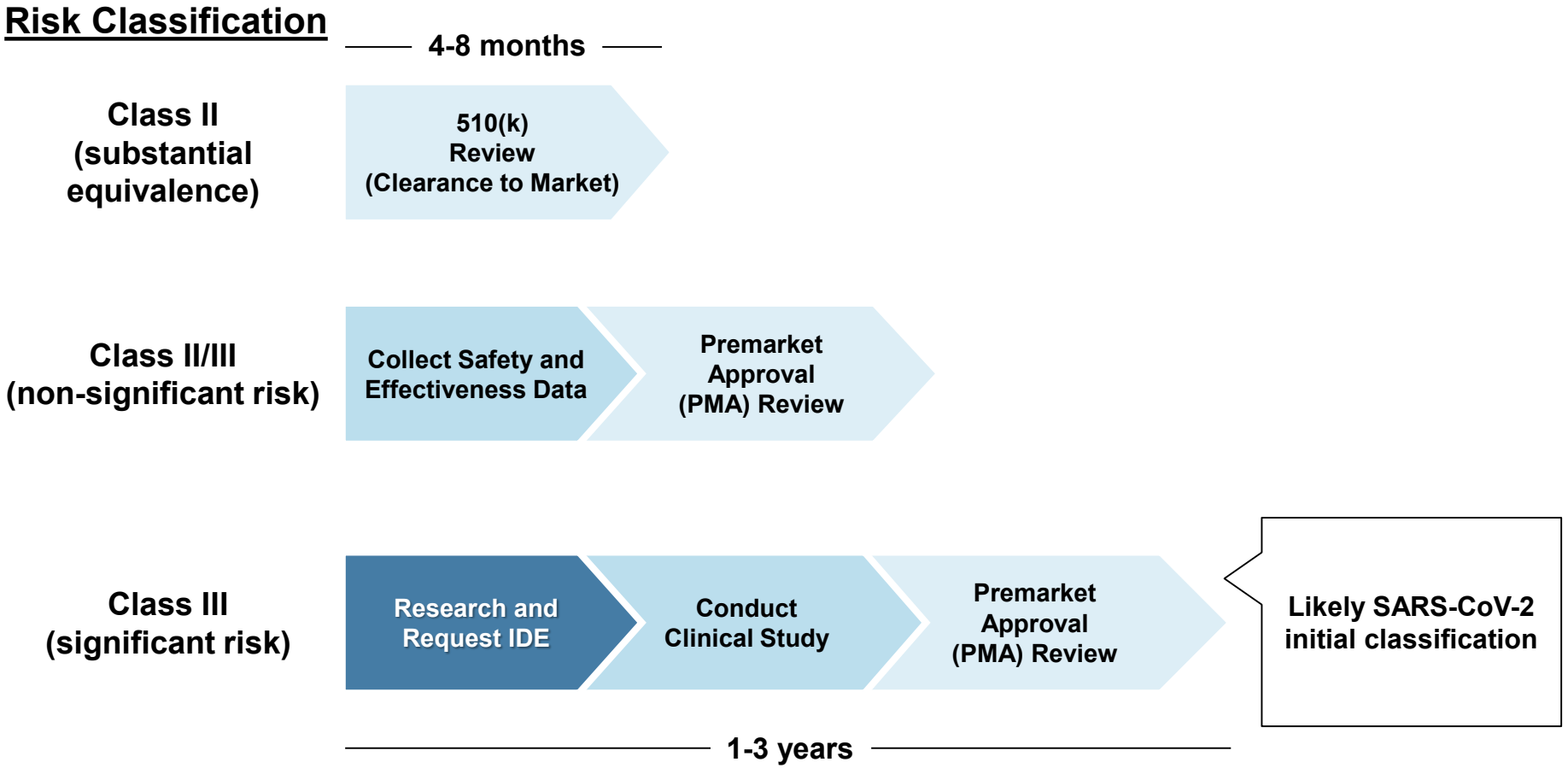
Average Timelines for Test Development

	Initial Development	Optimization	Validation	Regulatory Approval[1]
Molecular Test	~2-3 years			
	6-12 months	**~12-24 months**		**~6-12 months**
	• Once gene sequences (DNA, RNA) of interest are identified, making required reagents may be fast	• Multiple optimization parameters are considered but can be examined quickly	• Securing clinical samples for trials can be difficult	• Regulatory agencies review, may require additional data for final yes/no decisions
Immunoassay	~3-4 years			
	6-12 months	**~24-36 months**		**~6-12 months**
	• Choosing the target to detect can be difficult • Antibodies used to detect proteins are difficult to produce	• Multiple parameters are considered, and optimizing test performance is highly complex	• Securing clinical samples for trials can be difficult • Scaling up production of some reagents is time consuming	• Regulatory agencies review, may require additional data for final yes/no decisions

Note: 1- discussions with regulators are ongoing throughout entire process.
Source: Health Advances interviews and analysis.

Diagnostic Test Timeline: FDA Approval

Normally, it can take up to several years to complete the FDA regulatory process. The first fully validated Sars-Cov2 tests will most likely be Class III.

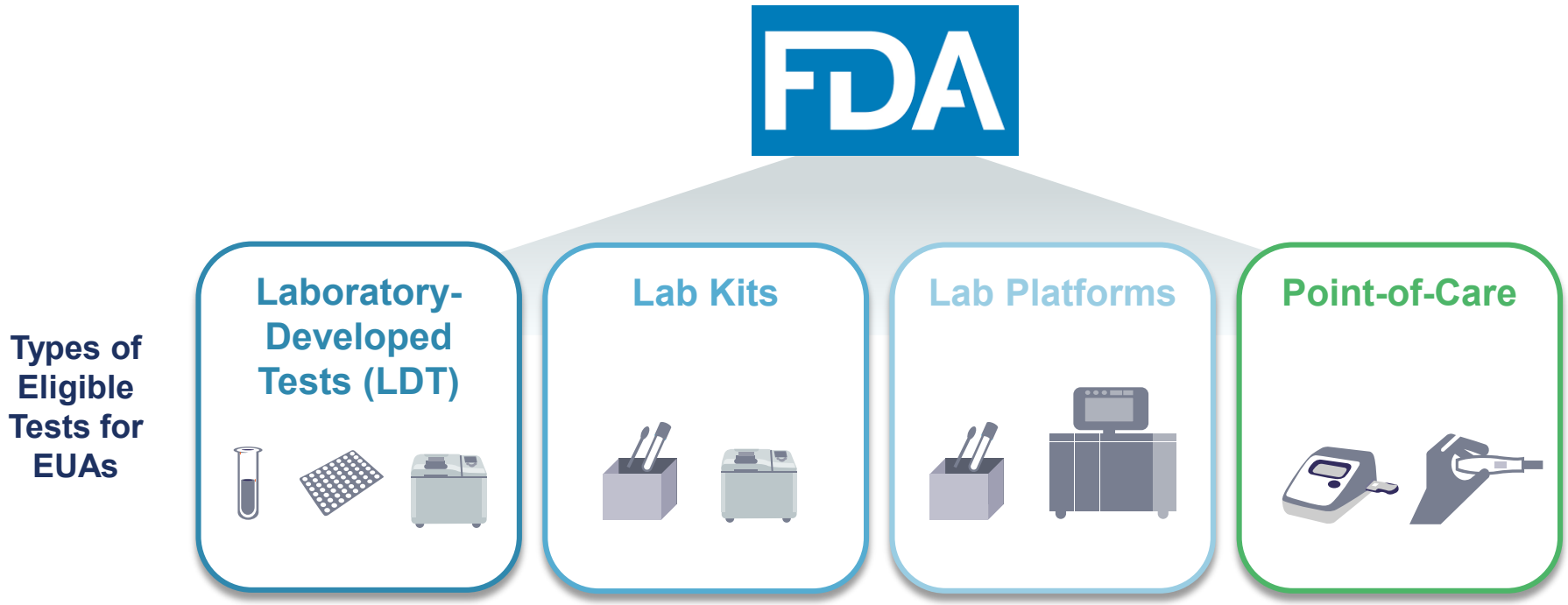


Note: IDE = investigational device exemption. Exempt devices and diagnostics typically have been excluded.
Source: Health Advances analysis, FDA, Orthopedics This Week 2014, MDUFA FY 2013 Performance Report, Medtech Insight.

US SARS-CoV-2 Dx Accelerated Path

During a public health threat, FDA can grant Emergency Use Authorization (EUA) to accelerate availability of unapproved/cleared tests as well as lab-developed tests (LDTs).

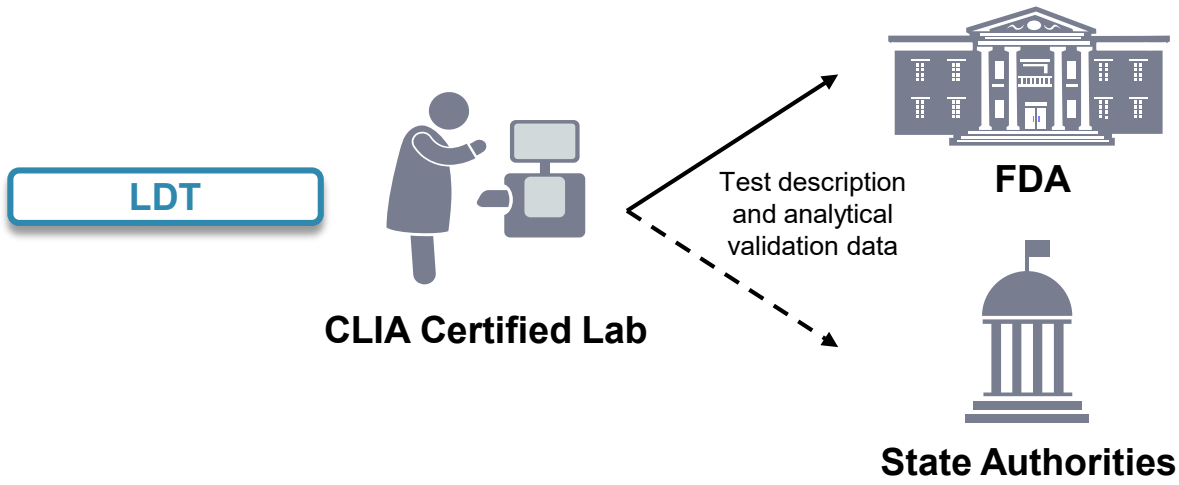
US Regulation of SARS-CoV-2 Tests: Emergency Use Authorizations (EUAs)



Source: Health Advances analysis, FDA, CMS.

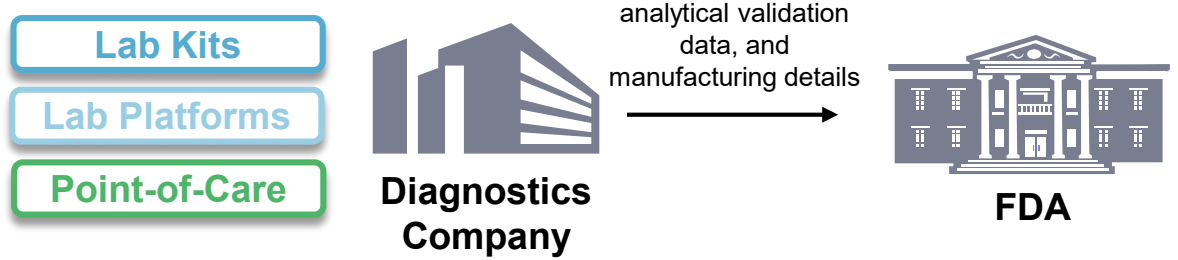
Accelerated EUA Process

New commercial test kits and platforms as well as LDTs for SARS-CoV-2 follow a similar process to submit technical and validation data to the FDA for an EUA.



Submission Process

- Upon validation, a data package is sent to FDA or state authorities
  - Must include analytical validation but no clinical data needed
- FDA reviews and grants EUA
- As of Feb 29, for Sar-CoV-2, labs could begin testing after validation and **before** FDA review

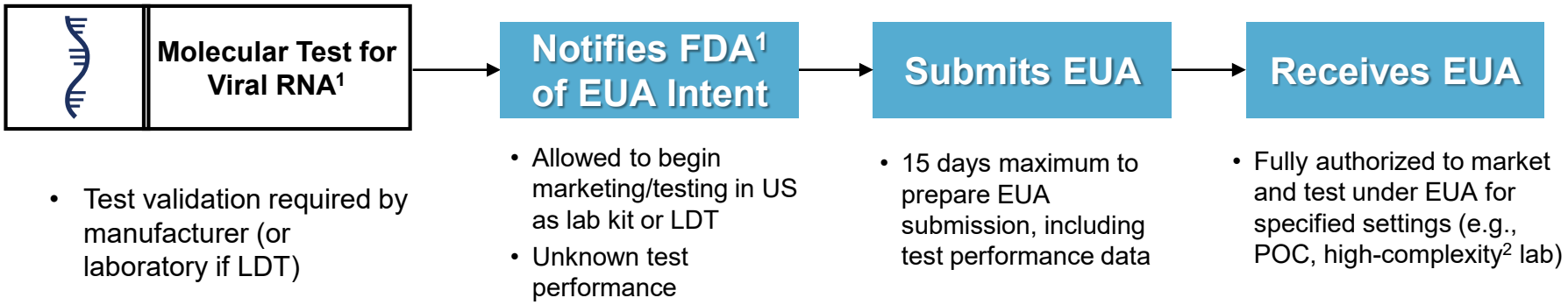


- Same as for LDTs
- As of Mar 16, companies can sell kits immediately after notifying FDA of a plan to submit an EUA as long as test is validated
- Some serology (antibody) tests require only minimal FDA notification and no data submission

Source: Health Advances analysis, FDA.

SARS-CoV-2 Regulatory Process: Molecular Tests

Adding complexity, EUA requirements are different for molecular and serology tests with molecular having a single clear path.



[1] FDA has granted authority for individual states who wish to authorize laboratories within that state to develop and perform tests to do so. In these scenarios, FDA notification is not necessary. States opting-in to this option are: Connecticut, Maryland, Mississippi, Nevada, New York, and Washington.

[2] Labs in the US are given a complexity designation (a program controlled by CMS under the CLIA legislation). High complexity labs are the most sophisticated and can perform the most complex testing. Moderate complexity are more common than high complexity, is the average lab. Waived indicates a setting that can perform POC testing only.

Source: Health Advances analysis, FDA, Genome Web.

SARS-CoV-2 Regulatory Process: Molecular Tests

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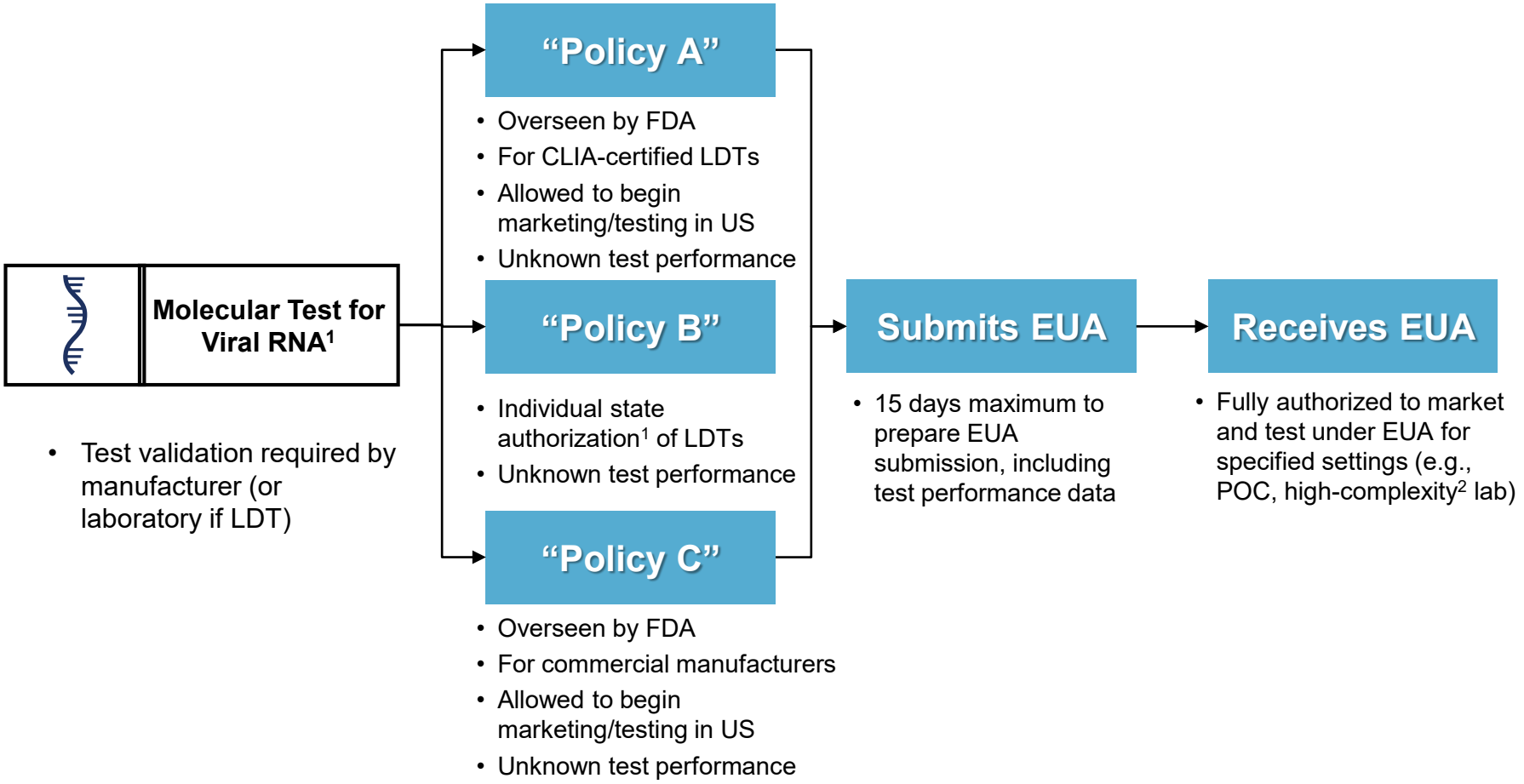

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Source: Health Advances analysis, FDA, Genome Web.

SARS-CoV-2 Regulatory Process: Serology Tests

More options exist for serology tests. These options are evolving regularly (most recent change 5/4/20) as FDA seeks to account for lower performing tests.

Immunoassays for Anti-SARS-CoV-2 Antibody

Test validation required by manufacturer or laboratory (if LDT)

Serology IVD "Umbrella"

- Tests can submit to interagency groups (e.g., NCI, NIH), rather than FDA, for evaluation

Test Evaluation

- Evaluated against strict performance metrics*

Receives "Umbrella" EUA

- Receives "umbrella" EUA for moderate- or high-complexity CLIA labs
- Provides standardized test performance comparison

"Policy A" or "Policy C"

- Overseen by FDA
- Policy A: for CLIA lab LDTs
- Policy C: for commercial manufacturers

Submits EUA

- 15 days maximum to prepare EUA submission, including test performance data

Receives EUA

- Fully authorized to market and test under EUA for specified settings (e.g., POC)

"Policy D"

- Overseen by FDA
- Specifically for serology tests (primarily commercial manufacturers) prior to or without EUA

Notifies FDA

- Notifies FDA of intent to market in US
- Unknown test performance

Submits and Receives EUA

- As of 5/4, required to submit EUA within 10 days
- FDA requires similar test performance requirements* as "umbrella" pathway

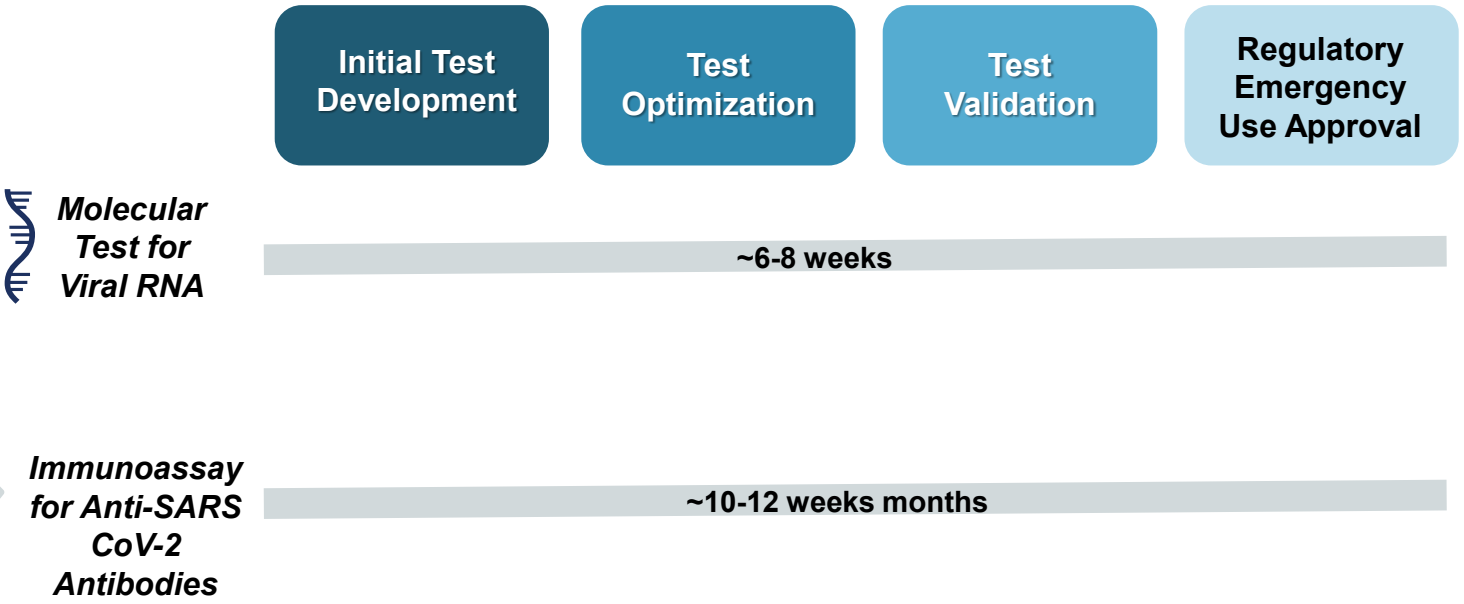
* Evaluation includes being run against a panel of samples from at least 30 positive samples and 80 negative or pre-COVID-19 samples, with 10/80 samples being HIV positive. Tests with both IgM and IgG must perform with overall 90% sensitivity, 95% specificity. Tests for IgM only must have at least 70% sensitivity, and tests with IgG only must have at least 90% sensitivity. All tests must show no cross-reactivity with HIV (an emerging concern with serology testing).

Source: Health Advances analysis, FDA, GenomeWeb.

Timeline of SARS CoV-2 Test Development and EUA

As a result, in times of emergency, the test development and regulatory approval timeline is shortened: 1-2 months for molecular tests and 2-3 months for immunoassays.

Timelines for Test Development Under EUA



Source: Health Advances interviews and analysis.

Steps to Build Manufacturing Capacity for Testing

In the normal pathway, after validation, companies typically increase production of tests incrementally over a period of time while ensuring that test kits are shelf-stable.

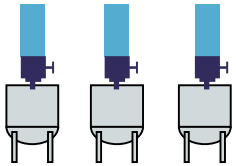
Step	Source Required Materials	Establish Manufacturing Lines	Produce and Distribute
Timeline	Days, Weeks, Months, Years	Days, Weeks, Months, Years	Days, Weeks, Months, Years
	• Secure steady, high-volume sources of needed (and approved) materials – E.g., reagents, controls, calibrators • Greater sourcing complexity for serologic tests due to biologic reagents (antibodies)	• Select[1] and/or build facility and allocate product lines[2] – Constructing and certifying new facilities may require 2-3 years – New certified line in existing facility takes 3-6 months – Convert existing lines to new test takes 2-4 months • Optimize production based on demand and shelf-life/stability	• Distribute kits in highly controlled logistics to ensure quality control (requires temperature control, chain of custody, etc.)

[1] Internal versus outsourced.
[2] A production line includes all workers, machinery, and automation processes required to produce a new test.

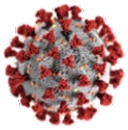
Source: Health Advances interviews and analysis.

Build Manufacturing Capacity: SARS-CoV-2 Challenges

In an emergency situation, companies are rushing to get to market leading to quality control issues and, in the case of SARS-CoV-2 facing additional outside challenges.



Step	Source Required Materials	Establish Manufacturing Lines	Produce and Distribute
Regular Timeline			
SARS-CoV-2 Timeline			



SARS-CoV-2 Challenges

Limited Source Materials

- Limited supply of validated reagents (e.g., extraction buffers) to include in kits
- Supply chain disruptions (e.g., no access to Chinese goods)

Time Crunch Leading to

- Limited QC
- Unknown shelf-life/stability of test kits

Distribution Delays

- Lack of coordination to decide which labs get what kits and when, leading to distribution delays

Source: Health Advances interviews and analysis.

Lab Implementation

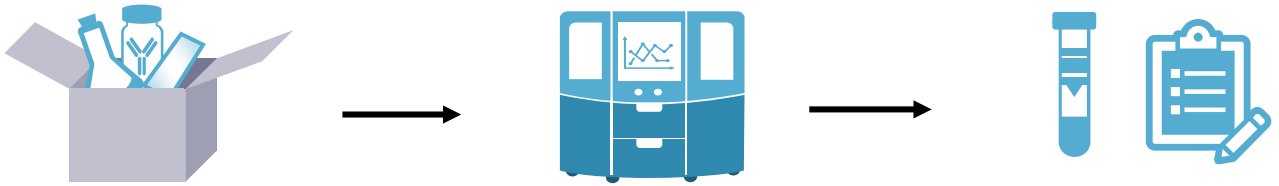
After a test is validated by the manufacturer and ready for use, labs still have to prepare to actually use the test.

	Test Development, Approval and Manufacturing	**Lab Implementation**	Provider Education and Adoption	Lab Management of Ongoing Testing Logistics
Description	• Design and ensure test works • Obtain approval to sell/use test	• Acquiring test components • Validating test works in specific lab		
Key Challenges	• Developing a test requires critical components (e.g., reagents, etc.) • Proving a test works requires patient testing • Approval and manufacturing require high investment	• New tests often require learning new processes • Labs have multiple tests and processes to consider beyond performing test • Understanding real-world test results can be complicated		

Source: Health Advances analysis.

Steps in Lab Implementation

Diagnostic test setup and validation must be carried out before it can be offered as a service, taking a minimum of 2-3 weeks but often several months to complete.



Step	Test Set-Up	Test Validation	Lab Prep for Patient Samples
Timeline	Days, Weeks, Months, Years	Days, Weeks, Months, Years	Days, Weeks, Months, Years
	• Test set up on instrument – May take several months (new instrument) – May require software updates or instrument changes • Controls verify known results • Lab personnel trained/ certified to process patient samples and run test	• Test validated for accuracy and reproducibility – Run minimum 50 pos/50 neg samples for validation (qualitative test) • Procedures established to maintain quality • Complete proficiency testing*	• Ensure sufficient supplies and personnel to run the test • Determine protocol for accepting/tracking samples and reporting data

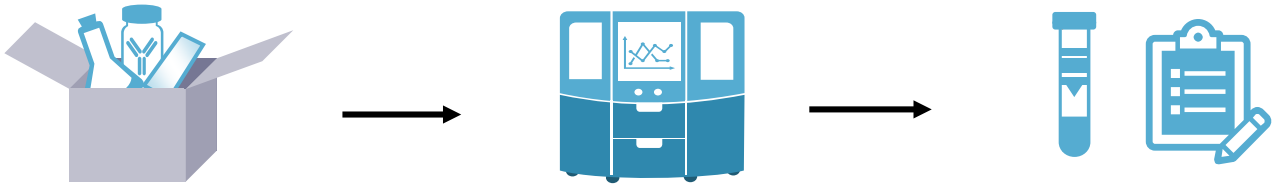
* Lab proficiency testing is where the lab tests unknown specimens from outside sources to ensure accurate results.

Note: Time duration is dependent on the lab expertise. Test validation includes a number of components, including verifying analytic accuracy, precision, sensitivity (lower detection limit), reportable range, reference intervals, and result interpretation.

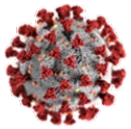
Source: Health Advances analysis, Archives of Pathology, CLSI.

Steps in Lab Implementation: SARS-CoV-2 Challenges

Given the time pressure to get tests up and running for SARS-CoV-2, labs have needed to find alternative, abbreviated methods for test validation.



Step	Test Set-Up	Test Validation	Lab Prep for Patient Samples
Regular Timeline	Days, Weeks, Months, Years	Days, Weeks, Months, Years	Days, Weeks, Months, Years
SARS-CoV-2 Timeline	Days, Weeks, Months, Years	Days, Weeks, Months, Years	Days, Weeks, Months, Years



SARS-CoV-2 Challenges

Time Crunch

- Must use existing platforms (no time to set up new instruments)
- Less well trained techs

Limited Choice in Test Used

Limited Validation

- Positive samples not easily obtainable
- Proficiency testing not possible

Unknown test accuracy

Insufficient Supplies/Staff

- Insufficient test supply (e.g., reagents, reference materials)
- Short-staffed for high influx of tests
- LIS integration steps may be skipped

Logistical hurdles and longer TATs

Note: LIS = Laboratory Information System
Source: Health Advances interviews and analysis.

Provider Education

Before testing can really take off, clinicians must be educated by lab personnel on how and when to use each test.

	Test Development, Approval and Manufacturing	Lab Implementation	**Provider Education and Adoption**	Lab Management of Ongoing Testing Logistics
Description	• Design and ensure test works • Obtain approval to sell/use test	• Acquiring test components • Validating test works in specific lab	• Educating providers on how and when to use the test • Setting up communication tools	
Key Challenges	• Developing a test requires critical components (e.g., reagents, etc.) • Proving a test works requires patient testing • Approval and manufacturing require high investment	• New tests often require learning new processes • Labs have multiple tests and processes to consider beyond performing test • Understanding real-world test results can be complicated	• Understanding real-world test results can be complicated • Guidelines for how and when to use a test evolve over time	

Note: EMR = electronic medical records.
Source: Health Advances analysis.

Provider Education and Adoption

Clinical staff must have guidelines and procedures on how to test patients and interpret results provided by the laboratory.

Healthcare Provider Questions to Answer

Testing Logistics

- What testing is available at my institution?
- When do I send out to another facility?
- Which of my patients are eligible for each test?
  - How do I allocate tests when there is a shortage?
- When do I use POC vs. lab testing?
- What sample types are required for each test type?
- How do I order testing?

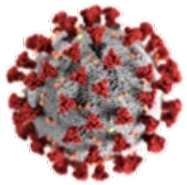
Lab Results

- When can I expect test results and how does the turnaround time affect my patient management?
- How do I interpret the results?

Source: Health Advances analysis.

Provider Education and Adoption: SARS-CoV-2 Challenges

HCPs face a multitude of challenges related to SARS-CoV-2, largely stemming from the lack of standardized information being relayed to them due to the time pressure to test.



SARS-CoV-2 Challenges

Testing Logistics	**Unknown Testing Labs/Locations**	• Labs capabilities changing daily • Unclear which labs are accepting samples from which providers
	Varying Patient Eligibility Criteria	• Hard to know which patients are eligible for testing, since criteria varies by lab and by state
	Test Ordering Delays	• Overwhelming testing demand in some regions causes ordering backlog of several days/weeks
Lab Results	**Lack of Clarity on Test Choice**	• Which test to order (molecular versus serology versus both) not always clear/ guidelines not always followed
	Uncertain Turnaround Time (TAT)	• Result TAT varies by day and by lab
	Inexperienced Result Interpretation	• HCPs lack experience interpreting test results given limited training due to time pressure

Source: Health Advances interviews and analysis.

Managing Ongoing Test Logistics

To keep a test running, labs must continue to do ongoing management of testing logistics throughout the service offering of a test.

	Test Development, Approval and Manufacturing	Lab Implementation	Provider Education and Adoption	Lab Management of Ongoing Testing Logistics
Description	• Design and ensure test works • Obtain approval to sell/use test	• Acquiring test components • Validating test works in specific lab	• Educating providers on how and when to use the test • Setting up communication tools	• Ensuring steady supply of test components and patient samples
Key Challenges	• Developing a test requires critical components (e.g., reagents, etc.) • Proving a test works requires patient testing • Approval and manufacturing require high investment	• New tests often require learning new processes • Labs have multiple tests and processes to consider beyond performing test • Understanding real-world test results can be complicated	• Understanding real-world test results can be complicated • Guidelines for how and when to use a test evolve over time	• Shortages of test components • Poor quality patient sample • Lab technicians to run tests

Source: Health Advances analysis.

Steps to Manage Testing Logistics

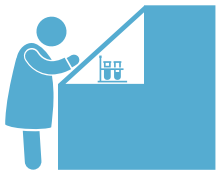
Several days are typically required to collect, perform and report lab test results. Patients in large hospitals with labs can potentially deliver same day or overnight results.

Step	Sample is Collected	Lab Performs Test	Physician Interprets Results
Timeline	Days / Weeks / Months / Years	Days / Weeks / Months / Years	Days / Weeks / Months / Years
	• Collection kits sent to doctor offices and lab sites – E.g., swabs, needles, tubes, collection vials, PPE • Sample* collected by technician (or self-collected) • Transported to lab (on-site or different location)	• Lab receives and logs sample for testing • Sample prep and analysis via manual or automated steps • Results recorded in EHR and reported to physician and/or patient	• Interprets lab results and other patient information – Makes medical recommendations and decisions • Patient receives test results in-person, by phone, or by electronic communication

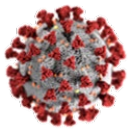
* A variety of sample types could be collected depending on the test, such as blood sample, stool, urine, nasal swab, etc.
Note: EHR = electronic health record, PPE = personal protective equipment.
Source: Health Advances analysis.

Management of Testing Logistics: SARS-CoV-2 Challenges

Several challenges, particularly in sample collection, exist for SARS-CoV-2 testing. Lack of readily available sample collection tools and testing delays make testing logistics difficult.



Step	Sample is Collected	Lab Performs Test	Physician Interprets Results
Regular Timeline	Days / Weeks / Months / Years	Days / Weeks / Months / Years	Days / Weeks / Months / Years
Accelerated Timeline	Days / Weeks / Months / Years	Days / Weeks / Months / Years	Days / Weeks / Months / Years



SARS-CoV-2 Challenges

Lack Proper Collection Kits

- Lack of collection swabs
- Specialized viral transport media (VTM) required for many tests but in low supply
- Limited phlebotomists available (for blood samples for serology)

Incorrect collection leads to inaccurate results (false negatives)

Time Crunch

- Technicians lack experience interpreting test results
- Lack robust quality control

Turnaround time delays and unknown result quality

Limited Experience

- Difficult selecting the right test
- Difficulty interpreting results (particularly for serology - potential immunity v exposure)

Incorrect patient managment

* Available sample types for SARS-CoV-2 testing include blood, saliva, and nasal/nasopharyngeal swabs.

Source: Health Advances interviews and analysis.

POC Test Development

Similar to lab tests, manufacturers must develop and validate a test to obtain regulatory clearance/approval to sell and use the test within the point-of-care (POC) setting.

Test Development, Approval and Manufacturing | POC Testing Site Implementation | Provider Education and Adoption | Site Management of Ongoing Testing Logistics


Description

- Design and ensure test works
- Obtain approval to sell/use test as POC
- Manufacture tests

Key Challenges

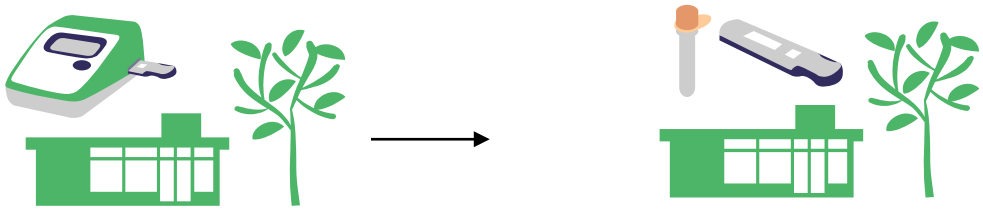
- Requires critical components (e.g., reagents, etc.)
- Must be simple enough for POC testing

- Similar development and regulatory process as lab tests
- POC tests need specific authorization to be run as POC via a CLIA-waived test
- Studies required may be more rigorous
  - Non-technicians need to be able to easily use tests in clinics, offices, or urgent care centers

Source: Health Advances analysis.

POC Test Implementation

Implementation of POC tests at non-lab sites is fairly simple given that these tests are designed to be as simple to use as possible, while maintaining accuracy and reliability.



Step	Test Set-Up	Site Preps for Patient Samples
Timeline	Days, Weeks, Months, Years	Days, Weeks, Months, Years

- Care sites (e.g., urgent care, retail, doctors office) purchase test kits and materials from manufacturers
- HCPs (e.g., nurses, PAs) receive training to run the POC test
- Practice determines testing and patient workflow

- No additional validation required
- Supervisor oversees testing to ensure test accuracy
- Supervisor ensures test materials (kits, collection swabs, etc.) are available for patient testing

* Sites that have a certificate of waiver from CLIA (Clinical Laboratory Improvements Amendments) can conduct human testing as long as the tests are CLIA-waived (otherwise known as point-of-care testing).

Source: Health Advances interviews and analysis, CLIA.

Provider Education for POC Tests

Clinicians must be educated on how and when to use POC tests, though this is generally an easier effort to coordinate given testing occurs on-site.

	Test Development, Approval and Manufacturing	POC Testing Site Implementation	Provider Education and Adoption	Site Management of Ongoing Testing Logistics
Description	• Design and ensure test works • Obtain approval to sell/use test as POC	• Setup POC test at non-lab sites • Obtain necessary test kits	• Educate providers on how and when to use the test • Set up communication tools (EMR link if available)	• HCP education similar but easier than for lab tests since testing is on-site • Short time to result (5-60 mins) simplifies test logistics and result interpretation (typically Yes/No answer)
Key Challenges	• Requires critical components (e.g., reagents, etc.) • Must be simple enough for POC testing	• Provide limited training for HCPs (nurses, PAs) to operate test	• Can be difficult to train all clinicians	

Note: EMR = electronic medical records.
Source: Health Advances analysis.

Ongoing Test Logistics for POC Tests

POC test results are reported in minutes to hours, and most of the logistics are centered around sample collection and test kit availability within that test site.

- Manufacturer sells/ distributes sample collection and test kits to non-lab sites
- Sample* collected from patient by HCP (typically nurse or PA)

- POC test performed on-site
- Results recorded in EHR and reported to physician and/or patient

- Physician interprets results and makes medical recommendations and decisions
- Patient receives test results in-person or via phone/email/telemedicine

* A variety of sample types could be collected depending on the test, such as blood sample, stool, urine, nasal swab, etc.

Source: Health Advances analysis.

Comparison of EUA Serology Tests (1 of 2)

Updated 5/5/2020

Roughly half of the EUA authorized serology tests target N antigens and the remaining S antigens. The lab automated EIA and ELISA options are more accurate than later flow.

Manufacturer	Ig Measured	Antigen Targeted	Measurement	Method Category	Sensitivity	Specificity	PPV*	NPV*
Abbott	IgG	N	Indirect	Automated CLIA/EIA	100%	99.6%	92.9%	100%
DiaSorin	IgG	S	Indirect	Automated CLIA/EIA	97.6%	99.3%	88.0%	99.9%
EUROIMMUN a PerkinElmer company	IgG	S	Indirect	ELISA	90%	100%	100%	99.5%
Ortho Clinical Diagnostics	IgG	S	Indirect	Automated CLIA/EIA	87.5%	100%	100%	99.3%
	Total Ig	S	Indirect	Automated CLIA/EIA	83.3%	100%	100%	99.1%
BIO-RAD	Total Ig	N	Indirect	ELISA	92.2%	99.6%	91.7%	99.6%
Roche	Total Ig	N	Indirect	Automated CLIA/EIA	100%	99.8%	96.5%	100%

* PPV and NPV measured at assumed prevalence of 5%.
Note: N = nucleocapsid, S = spike, EIA= enzyme immunoassay, CLIA = chemiluminescence assay, ELISA = enzyme linked immunosorbent assay.
Source: Health Advances analysis, FDA, company websites.

Comparison of EUA Serology Tests (2 of 2)

Updated 5/5/2020

Roughly half of the EUA authorized serology tests target N antigens and the remaining S antigens. The lab automated EIA and ELISA options are more accurate than later flow.

Manufacturer	Ig Measured	Antigen Targeted	Measurement	Method Category	Sensitivity	Specificity	PPV*	NPV*
Mount Sinai	IgG	S	Indirect	LDT; Automated or ELISA	92.5%	100%	100%	99.6%
Wadsworth Center NYSDOH	Total Ig	N	Indirect	LDT; Automated or ELISA	88.0%	98.8%	79.4%	99.4%
Autobio	IgG + IgM	S	Direct	Later Flow	88.1%*	99.0%*	82.9%	99.4%
CHEMBIO DIAGNOSTIC SYSTEMS, INC.	IgG + IgM	N	Direct	Later Flow	93.5%*	94.4%*	46.8%	99.6%
Cellex™	IgG + IgM	Unknown	Direct	Later Flow	93.8%	96.0%	55.2%	99.7%

* Sensitivity and specificity for combined IgG/IgM.
Note: N = nucleocapsid. S = spike. PPV and NPV measured at assumed prevalence of 5%.
Source: Health Advances analysis, FDA, company websites.

Health Advances Diagnostics Leadership Team

Donna Hochberg, PhD
Partner

- Donna Hochberg joined Health Advances in 2005 and leads the firm's Diagnostics and Life Science Tools Practice.
- Her work includes application prioritization, launch strategy, corporate strategy, deal diligence, and international and domestic market analysis using both qualitative and quantitative approaches. Her clients offer products and services in precision medicine, point-of-care, mainstream clinical diagnostic, and life science tools and range from small diagnostics and tools start-ups to the largest public companies and non-profit institutions in the industry.
- Prior to joining Health Advances, Donna worked as a scientist at One Cell Systems and Iquum developing diagnostics for oncology and infectious diseases. She received her Bachelors degree in Biology from the University of Illinois at Urbana-Champaign and her Ph.D. in Immunology from the Sackler School of Biomedical Sciences at Tufts University

Gary Gustavsen
Partner and Managing Director

- Gary Gustavsen came to Health Advances in 2005 and leads the Precision Medicine Practice at Health Advances. His work focuses on commercialization strategy, indication prioritization, pricing and reimbursement strategy, system economics, and business development opportunities for both diagnostic and therapeutic clients.
- Prior to joining Health Advances, Gary was a researcher at Brookhaven National Lab evaluating a proprietary line of synthetic growth factors. Gary also worked in the Cell & Tissue Technologies group at Becton Dickinson, the Exploratory Cancer Research group at OSI Pharmaceuticals, and most recently the Corporate Strategy group at Millennium Pharmaceuticals. Gary received his Bachelors degree in Biomedical Engineering from Duke University and his Masters degree in Biomedical Engineering from Stony Brook University.

Health Advances Diagnostics Leadership Team

Kristen Amanti, PhD

Vice President

- Kristen Amanti joined the Health Advances team in 2010 and is a leader in the Reproductive and Genomic Health practice and Precision Medicine practice. She has deep experience in commercialization strategy, business development opportunity assessment, deal diligence, international and domestic market assessment, corporate strategy, and is a seasoned workshop facilitator. She has content expertise in companion diagnostics, reproductive and prenatal health, genomic health, cancer screening, tumor genetics and oncology.
- Prior to joining Health Advances, Kristen received her PhD in Cancer Pharmacology from Dartmouth College where her research focused on the development of novel targeted cancer therapeutics. She received her Masters degree in Cell and Molecular Biology and Bachelors degree in Biology from the University of Vermont.

Peter Origenes

Vice President

- Peter Origenes brings over 30 years of healthcare experience to Health Advances, including as a corporate executive, principal investor, and strategy consultant across diagnostics, life science research products, medical devices, and biopharmaceuticals.
- Prior to joining Health Advances, Peter held executive positions at Becton Dickinson, GE Healthcare, and Ortho Clinical Diagnostics. Prior to that, he was a partner at Radius Ventures, and a consultant with The Wilkerson Group and Bain.
- Peter holds a Master of Science in Industrial Administration from the Tepper School at Carnegie Mellon University, and Bachelor's degrees in Genetics and History from the University of California, Berkeley.

Kristine C. Mechem PhD

Vice President

- Kristine Mechem has over 15 years of life science experience across diagnostics, medical devices and therapeutics. Her experience spans the full continuum of commercial activities from market planning to sales force effectiveness. She has expertise in portfolio prioritization, product requirements, asset opportunity assessments and launch planning.
- Most recently she was the commercial head of a micro-cap molecular diagnostic company. At OncoCyte, she helped to take the company public, served as a corporate officer and led the development of the commercial plan. She has also held positions at Abbott, Genentech and The Zitter Group
- Kristine received her PhD in Sociology from the University of Chicago. She is an active member of Women In Bio.

Health Advances Diagnostics Leadership Team

Arushi Agarwal
Vice President

- Arushi Agarwal joined the Health Advances team in 2011 and spends the majority of her time working in the Diagnostics and Life Sciences Practice. She has expertise in M&A due diligence and global commercialization strategies for diagnostics. Arushi's specific areas of focus include companion diagnostics, point-of-care diagnostics and liquid biopsy testing.
- Prior to joining Health Advances, Arushi received her Masters in Biomedical Engineering from Columbia University and Bachelors in Biology from the Massachusetts Institute of Technology.

Daniela Hristova-Neeley, PhD
Director

- Daniela is an experienced team leader with expertise in opportunity assessment, global commercialization strategy, market access, and business model evaluation across diagnostics and life sciences products. Daniela's diverse experience in the diagnostics and life sciences tools space provides a strong base to help generate actionable growth strategies for clients.
- Prior to joining Health Advances, Daniela helped clients in the healthcare industry optimize their value proposition and global market access strategies to enable product adoption.
- Daniela earned her PhD in Chemistry, summa cum laude, from the University of Basel, Switzerland and her MBA from Johnson Graduate School of Management at Cornell University.

Health Advances Diagnostics Team

Laura Gullet
Engagement Manager

- Laura Gullett joined Health Advances in 2016 and works in our Diagnostics and Life Science Tools Practice.
- Her work focuses on commercialization strategy for both routine and specialty diagnostics across the US, Europe, and emerging markets. Her specific expertise includes laboratory and point-of-care diagnostics for infectious disease, oncology, and rare disease.
- Prior to joining Health Advances, she graduated magna cum laude from Harvard University with a BA in Chemistry & Physics.

Ravi Amin
Engagement Manager

- Ravi Amin joined Health Advances in 2014 and is an experienced team leader in the firm's Diagnostics and Life Science Tools Practice.
- His experience includes opportunity assessment, commercialization strategy, and market analysis with experience developing strategies for clients of all sizes
- Prior to joining Health Advances, Ravi worked at Beckman Coulter in corporate strategy and strategic marketing. He received his Bachelors in Genetics from the University of Georgia and his Master of Business and Science at the Keck Graduate Institute of Applied Life Sciences

Kelsey Taylor, PhD
Engagement Manager

- Kelsey Taylor joined the Health Advances team in 2016 and is an experienced team leader across Health Advance' Diagnostics, Biopharma, and Precision Medicine Practices.
- Kelsey's experience includes opportunity assessment, business model evaluation, and commercialization strategy development for novel diagnostics.
- Prior to Health Advances, Kelsey received her PhD in Biological and Biomedical Sciences at Harvard University and Bachelors in Biochemistry, Cellular and Molecular Biology from Connecticut College.

Emily Kong
Consultant

- Emily Kong joined Health Advances in 2016 and is a team leader across firm's Diagnostics, Digital Health, and Precision Medicine Practices
- Her experience includes development and commercialization strategy, competitive assessment, market sizing, and revenue forecasting with a content focus in several areas including oncology, precision medicine, traditional laboratory diagnostics, and rare diseases
- Prior to joining Health Advances, Emily received her Bachelors in Biology and Economics from Dartmouth College

Health Advances Diagnostics Team

John Latimer
Senior Analyst

- John Latimer joined Health Advances in 2018 and works primarily in the firm's Diagnostics and Life Sciences practice.
- He has experience in strategy development, international and domestic market analysis, M&A diligence, and opportunity assessment of emerging technologies.
- Prior to joining Health Advances, John graduated from Stanford University with a B.S. in Biology. He held several research positions during his time at Stanford including as a clinical researcher in the Department of Cardiovascular Medicine.

Aaron Dy, PhD
Senior Analyst

- Aaron Dy joined Health Advances in 2019 and works across healthcare practices, with a particular focus in the Diagnostics and Life Sciences Tools practice.
- His experience includes competitive assessment, commercial strategy, product positioning strategy, survey design, and revenue forecasting.
- Prior to Health Advances, Aaron received his Bachelors degree in Applied Physics from Indiana University and his PhD in Biological Engineering from the Massachusetts Institute of Technology.

Emily Berghoff, PhD
Senior Analyst

- Emily Berghoff joined Health Advances in 2020 and works across the firm's Diagnostic, MedTech, and BioPharma practices.
- Her experience includes opportunity assessment, commercialization strategy, market analysis, and revenue forecasting.
- Prior to Health Advances, Emily worked at Exosome Diagnostics developing assays for oncology. She received her PhD in Biological Sciences from Columbia University and her Bachelors degree in Chemistry from Colby College.

Alexis Froistad
Analyst

- Alexis Froistad joined Health Advances in 2019 and works across healthcare practices, with a focus in the Diagnostics and Life Sciences Tools practice.
- Her experience includes product positioning strategy, franchise development strategy, market analysis, and survey design.
- Prior to Health Advances, Alexis graduated from Stanford University with a B.S. in Human Biology. She held a long-term research position in the Stanford Parker Center for Allergy and Asthma Research studying pulmonary arterial hypertension.

Alexandra Dekkers
Analyst

- Alexandra Dekkers joined Health Advances in 2019 and works across healthcare practices, focusing in the Diagnostics and Life Sciences Tools practice
- Her experience includes market analysis, opportunity assessment, and product positioning strategy across geographies and practice areas
- Prior to Health Advances, Alexandra graduated from Georgetown University with a B.S. in Human Science, completing her senior research on vaccination rates and disease incidence for measles, mumps, and rubella.

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