December 2020

Diagnostic Testing for COVID-19

Partners In Health

Context for these materials

The ideas and testing methods presented in this deck reflect the latest public health thinking and scientific evidence as of December 2020. You are advised that the COVID-19 testing landscape remains highly fluid, and it is your responsibility to ensure that decisions are made based on the most up-to-date information available.

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Overview

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- **Overview of test types**
- Choosing a test type
- Population-based testing strategies
- Rapid antigen testing: uses and challenges
- Addressing inequities in testing
- Outstanding questions
- Appendix

There are two general categories of COVID-19 tests – molecular and serology

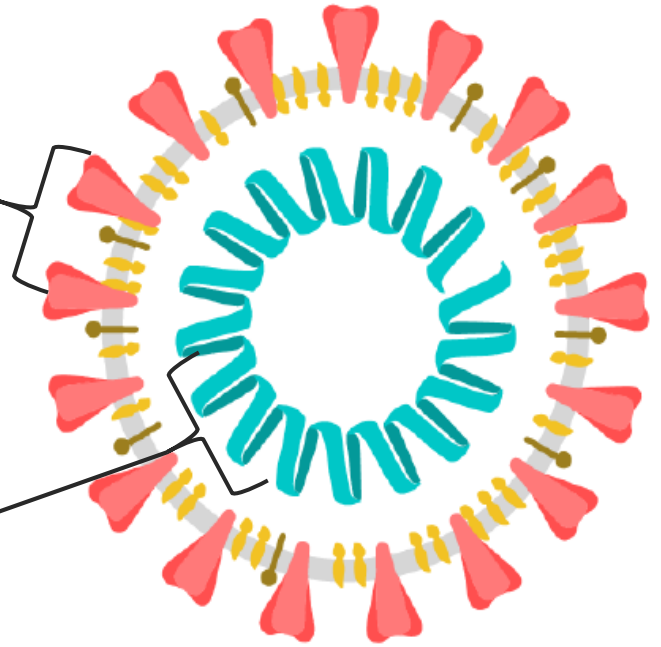
Molecular Test	Serology Test
• Detects active shedding of virus and in general, one should take steps to quarantine or isolate from others, especially with ongoing symptoms • Currently two types of molecular tests which directly detect the virus (see next page): 1. Nucleic Acid tests, such as RT-PCR tests, that detect the virus's genetic material 2. Antigen tests that detect specific proteins on the surface of the virus • Detection of virus does not necessarily confer infectivity, but it is suggestive	• Looks for antibodies in the blood that are made by the immune system in response to the virus to help fight infections. • Antibodies can take several days or weeks to develop after the onset of infection and may stay in the serum for weeks/months or more after recovery. Because of this, antibody tests are not generally used to diagnose an active coronavirus infection. • At this time, researchers do not know if the presence of antibodies means that you are immune to the coronavirus in the future.

https://www.centerforhealthsecurity.org/resources/COVID-19/serology/Serology-based-tests-for-COVID-19.html

Molecular tests can be further classified into antigen or nucleic acid tests

Antigen tests detect physical components of the virus, such as the surface proteins on the outer layer, or nucleocapsids inside the virus

Nucleic Acid tests, such as RT-PCR, detect the genetic material of the virus – often RNA – and therefore require "breaking open" the virus to obtain the genetic material inside



https://docs.google.com/document/d/1tDc622k8YHW2izTsTBTSR1Gf7UQuK_DtylWgOvgi36s/edit

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- Appendix

Choice of test may depend on the reason for testing…

1 Diagnosis

- Aims to identify current infection in individuals and is performed when a person has signs or symptoms consistent with COVID-19, or when a person is asymptomatic but has recent known or suspected exposure to SARS-CoV-2.
- Examples of diagnostic testing include testing symptomatic persons, testing persons identified through contact tracing efforts who were exposed to someone with a confirmed or suspected case of COVID-19.

2 Screening

- Aims to identify infected persons who are asymptomatic and without known or suspected exposure to SARS-CoV-2.
- Performed to identify persons who may be contagious so that measures can be taken to prevent further transmission.
- Examples of screening include testing in congregate settings, such as a long-term care facility or a correctional facility, a workplace testing its employees, or a school testing its students, faculty, and staff.

3 Surveillance

- Aims to monitor population-level infection and disease, or to characterize the incidence and prevalence of disease.
- Performed on de-identified specimens, and thus results are not linked to individuals; results of surveillance testing are only returned in aggregate. Thus, surveillance testing is not used for individual decision making, but rather population interventions.
- An example of surveillance testing is a plan developed by a state public health department to randomly select and sample a percentage of all persons in a city on a rolling basis to assess local infection rates and trends.

Source: CDC - https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html

…with different tests better suited for different purposes

	Key elements of a test needed:	*Test type suggestions:*
1 **Diagnosis**	• Accuracy (Sensitivity & Specificity) • Speed	• Perhaps prioritize molecular tests for clinical accuracy • If speed becomes a barrier to taking clinical or epidemiological actions, consider expanding to antigen testing
2 **Screening**	• Accuracy (Sensitivity & Specificity) • Speed • Scale/Volume/Cost	• Antigen testing if done at high frequency • Prioritize point-of-care rapid tests for screening events to reduce loss-to-follow up (e.g. rapid antigen tests, or rapid molecular tests like IDnow)
3 **Surveillance**	• Scale/Volume/Cost • Logistical convenience	• Antigen testing for surveillance of active cases • Antibody testing for seroprevalence studies; dried blood spot sample collection eases sample collection/transport

Population screening is distinct from diagnostic testing and requires a new set of considerations

Screening Criteria	Broad sampling of asymptomatic people generally where they work or live and not in testing facilities
Payment	Screening should be free to the individual and paid for by employers, schools, or government
Procedure	Since screening may be frequent, self-administered saliva, anterior nares, or oral swabs would be preferred. Dried blood spot for antibody testing.
Technology	Requirement for high throughput, high accuracy, and low cost testing. *See pooled testing options in appendix.*
Logistics	End to end reliability and data transfer is critical to ensuring data integrity and efficiency of screening program
Supply Chain	Reliable raw material supply and manufacturing capacity to meet what will be an enormous global demand

What to look for when evaluating a test

- **Pretest probability** is the chance that the patient has the disease, estimated before the test result is known based on the probability of the suspected disease in that person given their symptoms.
    - At the population level, the pretest probability is also known as the ***prevalence***: the number of known cases of the disease in a population at a given time
- **Posttest probability** tells us a person's chance of having a disease after a test is performed, and more important for clinical use to decide whether to accept a diagnosis of disease, rule one out or order more testing.
- **Sensitivity** is the ability of a test to correctly identify the disease in the population of people who have the disease
    - ➢ *The closer to 100% sensitivity, the better the test is at detecting the virus (fewer false negatives)*
- **Specificity** is the proportion of people who test negative for the disease among those who do not have the disease.
    - ➢ *The closer to 100% specificity, the less likely the test is to have false positives*

Test Result	Patient has disease	Patient does not have disease
Positive	True Positive	False Positive
Negative	False Negative	True Negative

Click here to visit the source document and read more information here with examples.
Click here to practice calculating these values with an online calculation tool.

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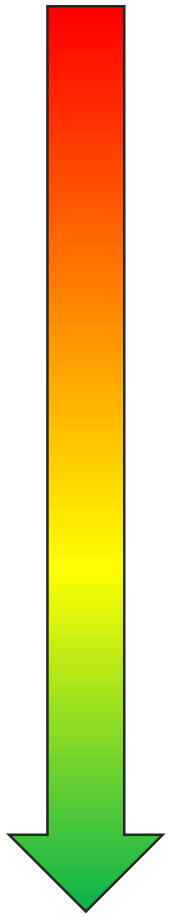
- Appendix

Testing strategies should match the population risk level



Risk level

Population

Symptomatic people

Exposed contacts

Healthcare workers

Nursing home residents and staff

Congregate living settings

Service sector/essential workers

Students and teachers

Public housing/Senior buildings

Offices

Asymptomatic general population

We will discuss recommendations for these populations in three main categories:

1) **high risk**
2) **medium risk**
3) **lower risk**

All testing should be complemented with essential community mitigation strategies:

- Daily or day-of symptom screening
- Mask wearing
- Hand washing
- Social distancing

Testing recommendations – high risk groups

Risk Level	• High
Populations	• Symptomatic people • Exposed contacts
Current Testing Strategy	• Molecular (mostly PCR) diagnostic testing available through community testing locations, physician's offices, hospitals, private pharmacies, etc. • All exposed contacts referred for immediate testing via contact tracing team
Ambitious/ 'Phase 2' strategy	• No technology change required → Continue to prioritize molecular (PCR) diagnostic testing for high sensitivity/specificity • Need to improve turnaround time for results within 24 hrs

Considerations	• To achieve faster TAT, consider:
	  ○ Amending current lab contracts to require turnaround time metrics / data reporting
	  ○ Engaging new vendors with extra capacity/faster TAT
	  ○ Procuring molecular tests with faster TAT (e.g., Abbot IDnow, CRISPR)

Testing recommendations – medium risk groups

Risk Level	• Medium
Populations	• Healthcare workers, Nursing home residents/staff, Congregate living settings, Service sector/essential workers, Students and teachers, Public housing/Senior buildings
Current Testing Strategy	• Return to work testing for some public sector employees • Nursing home testing through state and local health departments • Ad hoc testing events at public housing locations/senior buildings/shelters/etc.
Ambitious/ 'Phase 2' strategy	• Introduce weekly screening tests targeting random samples of each population • Emphasis on immediate/same day TAT of results to isolate and contact tracing any positives → Introduce rapid antigen testing as "entrance" tests
Considerations	• FDA EUA restrictions on rapid antigen testing of asymptomatic individuals • Prioritize tests with easy sample collection → Saliva, oral, nasal self-swabs • Pooled sampling could be leveraged to increase overall test capacity • Policy shaping at the state level to determine what tests are covered by insurance, so asymptomatic contacts and other asymptomatic individuals qualify for testing

Testing recommendations – lower risk groups

Risk Level	• Low
Populations	• Office workers, other (asymptomatic) general population
Current Testing Strategy	• Return to work testing for some public sector employees • Molecular (mostly PCR) diagnostic testing available through community testing locations, PCPs, hospitals, private pharmacies, etc.
Ambitious/ 'Phase 2' strategy	• Broad testing and outbreak surveillance, e.g., waste-water testing • Not priority for additional testing interventions if asymptomatic • Re-evaluate if/when at-home test kits become widely available
Considerations	• Reduce pre-test prevalence as much as possible (symptom screening, sanitation practices) to reduce false negative rate if using lower sensitivity tests, e.g., antigen tests • Need to ensure access to testing for the general/asymptomatic population is maintained at community testing sites, regardless of insurance or immigration status • Candidates for surveillance

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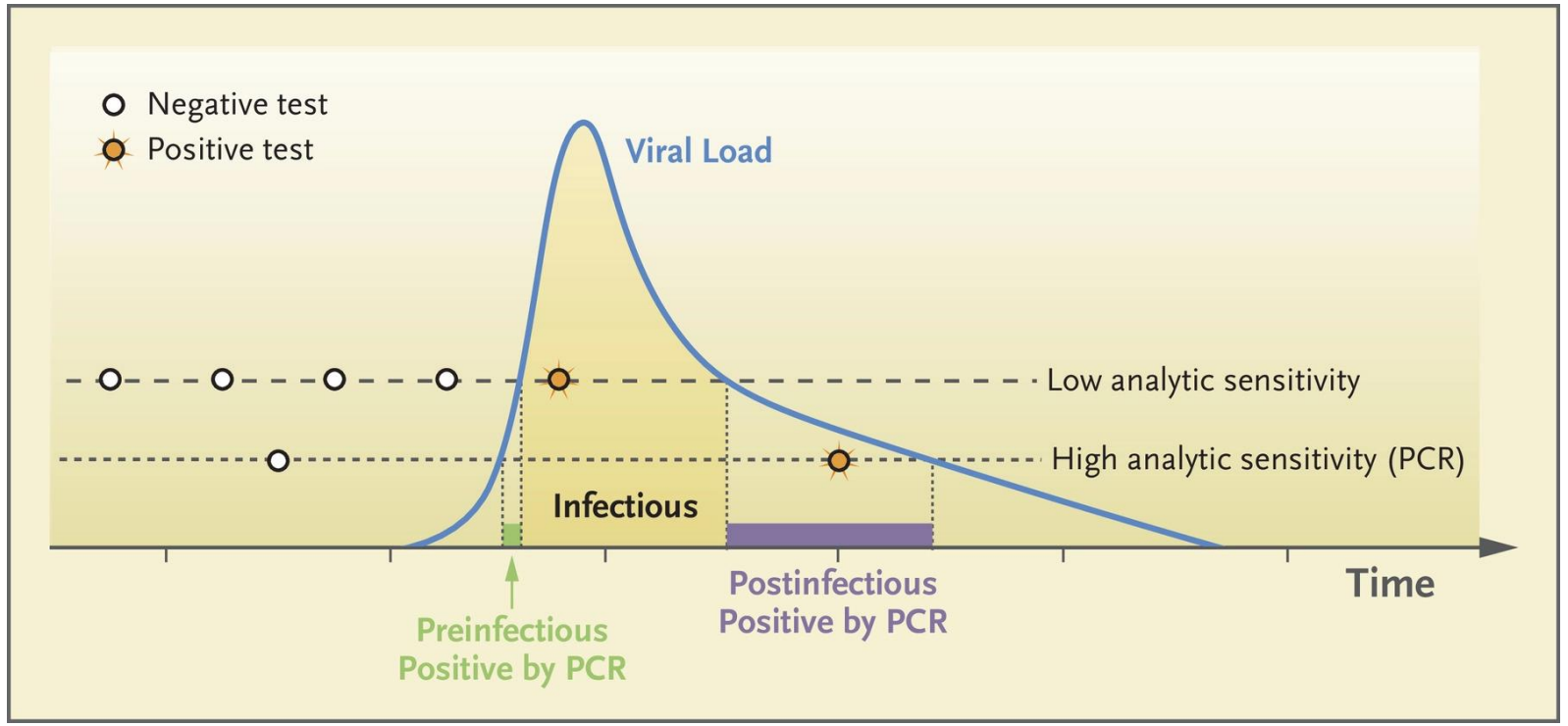
- Appendix

Emerging view: antigen tests have a lower sensitivity but may better determine infectivity

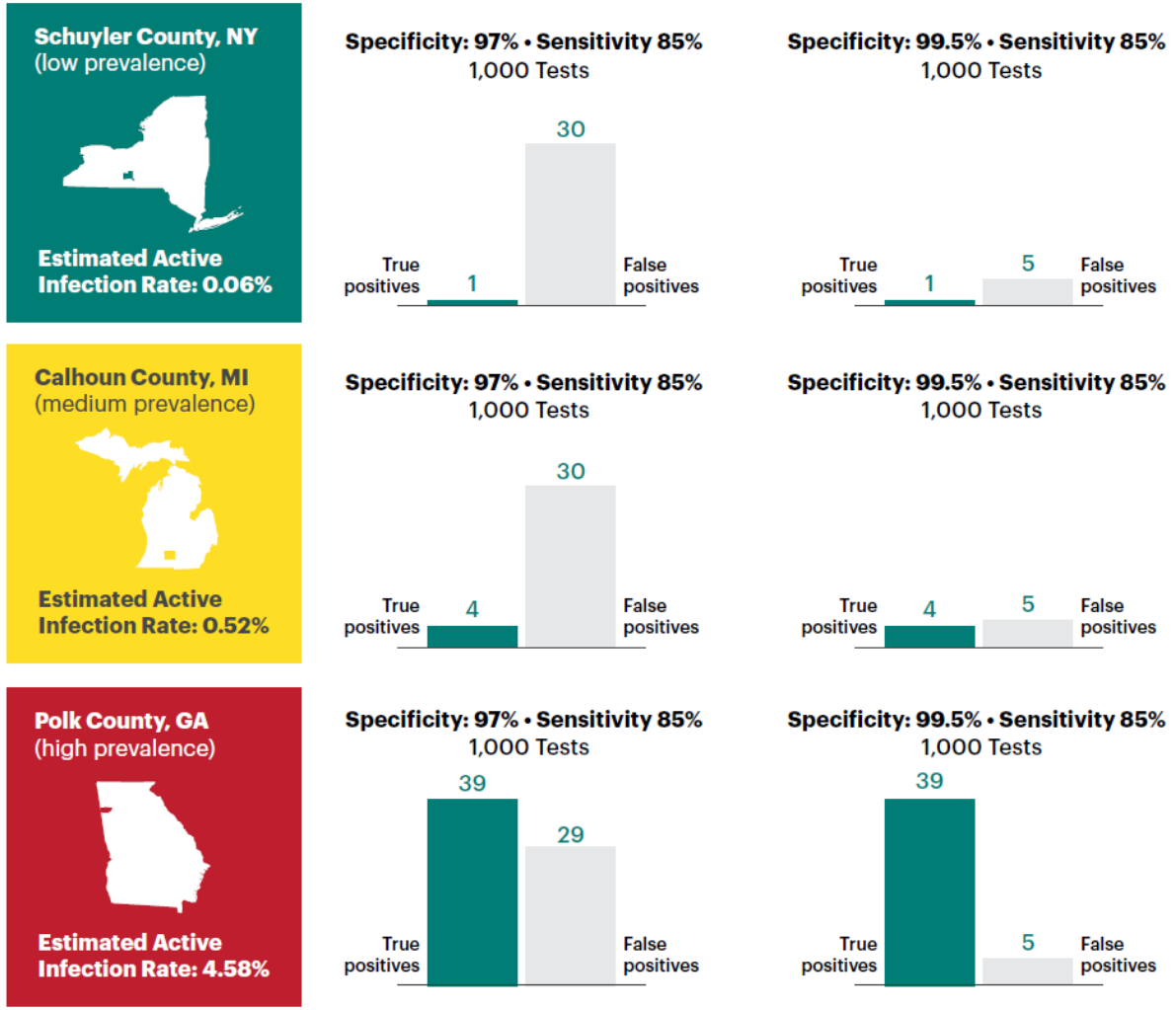


- The infections that lower sensitivity antigen tests are more likely to “miss” likely represent lower viral loads
- With other viruses (such as HIV), low or suppressed viral load corresponds significantly reduced transmission
- If this pattern holds true with Covid-19, most positives that antigen tests miss will be people who are less contagious. This is represented by the green and purple sections in the diagram on the left
- Additionally, since most Covid-19 antigen tests are designed to detect the Spike viral protein, which binds to target cells, no detetection may confer less transmission

https://www.nejm.org/doi/full/10.1056/NEJMp2025631

Rapid antigen testing has different accuracy based on the population of interest

With low specificity, false positive rates are relatively high



With most current Ag tests; however, false positives are low, but can represent a high proportion of postive results depending on pre-test prevalence

https://www.rockefellerfoundation.org/report/a-national-decision-point-effective-testing-and-screening-for-covid-19/

Even if the sensitivity is low in real world use, antigen testing can still effectively rule out disease

Specificity 99%, sensitivity estimated at **80%**. 500 people screened.

Test Result	Positive	Negative
Test Positive	40	4.5
Test Negative	10	445.5
10% Prevalence	50	450

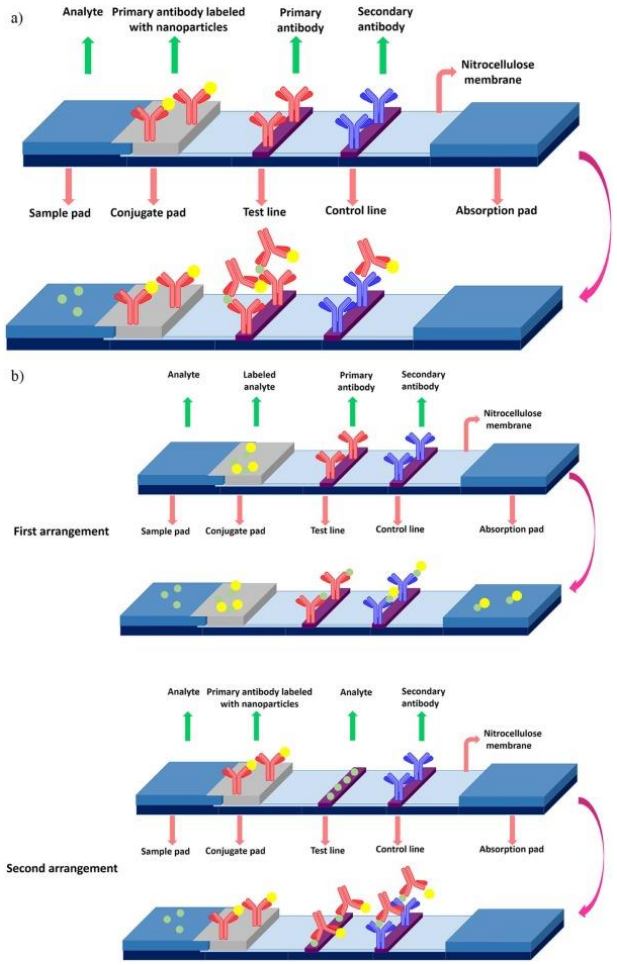
With high prevalence, there will be 10 people with the disease out of 500 who tested negative with a 2% false negative rate

Test Result	Positive	Negative
Test Positive	8	4.9
Test Negative	2	485.1
2% Prevalence	10	490

With low prevalence, there will be 2 people with the disease out of 500 who tested negative with a 0.4% false negative rate

With antigen tests, technology is widely available, supply chain is robust, and demand will be high

- No evidence of mutation affecting test characteristics
- There will be a number of large and small manufacturers of rapid antigen testing
- There may be minor supply chain issues not in terms of raw materials but in terms of assembly (with the exception of nitrocellulose)
- Projection of up to 20 million tests per day in the US



A Cheap, Simple Way to Control the Coronavirus

With easy-to-use tests, everyone can check themselves every day.

By Laurence J. Kotlikoff and Michael Mina

Nevada Revokes Halt on Rapid Antigen Testing in Nursing Homes

The reversal came just hours after the federal government threatened the state, calling the prohibition on the tests "illegal."

Specific challenges with rapid antigen testing

Issues

- Antigen tests have been authorized by the FDA for diagnostic use in symptomatic patients, but providers should confirm negative results with a PCR test if the pretest probability of infection is high (*see slide 10*)
- Antigen tests may be useful for screening if performed on a regular and frequent basis, e.g., every few days. This is to correspond to the 5-day period when viral shedding is highest (between Days 3 and 8 of infection) and thus tests are most effective
- Operator errors may have contributed to recent reports of false positives in some settings

Public Health Considerations

- Health departments may discourage use of antigen tests for one-time screenings given low positive predictive value
- Consider advising facilities against moving nursing home patients to COVID-19 wards until an antigen screening test is confirmed
- In communities where transmission rates are low and mitigation efforts are effective, PCR testing may be a more reliable approach to screening due to false positive and negative rates
- Training of personnel is critical to reduce false positives

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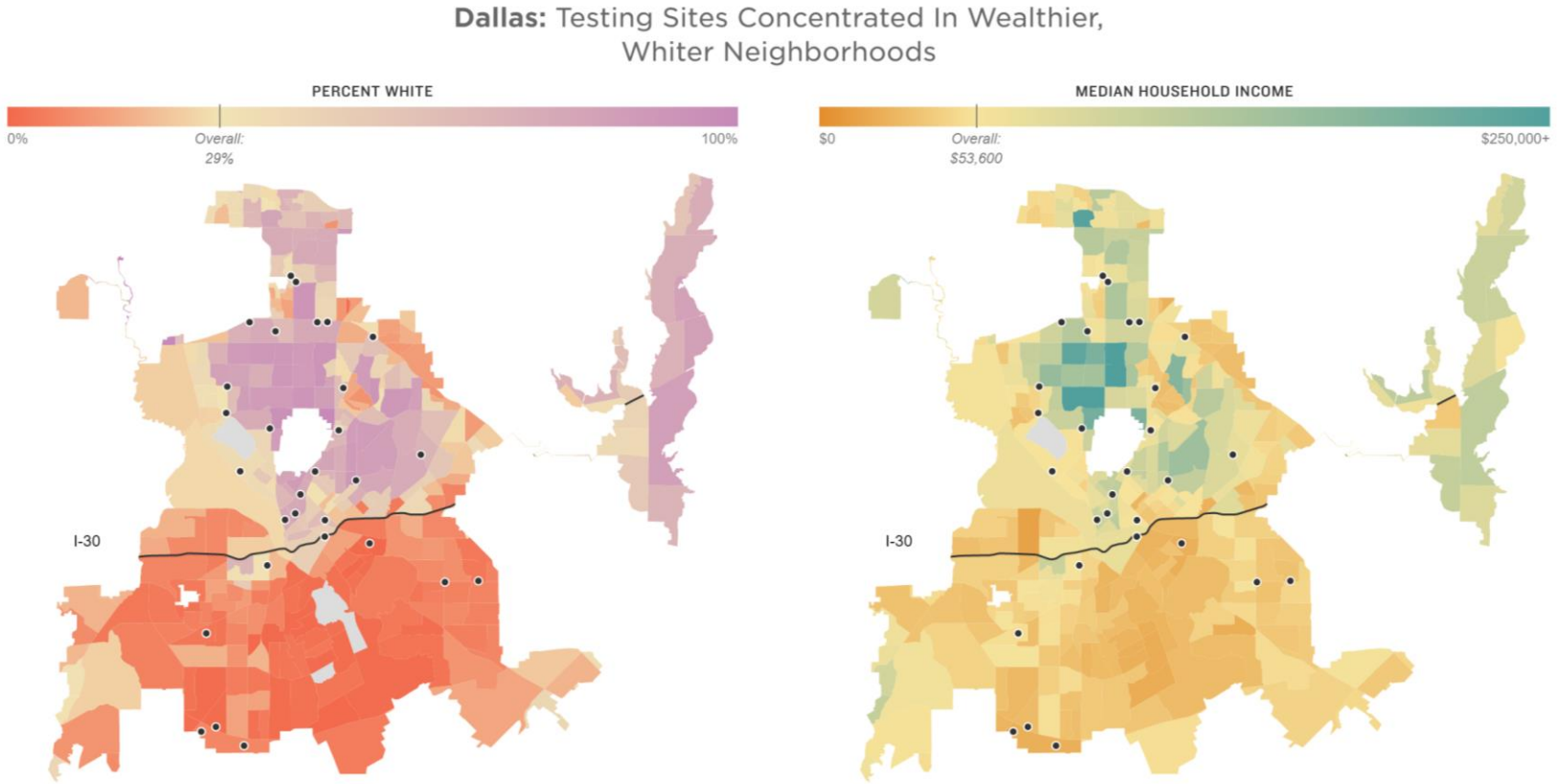
- Outstanding questions
- Appendix

There are significant disparities in access to testing for communities of color

- Governments often concentrate testing sites in whiter, wealthier communities
- For example, in Texas testing sites are disproportionately located in predominantly white areas
- In general, communities of color have a higher proportion of positive cases and have higher demand for testing. This results in longer wait times, longer turn around times and increased transmission



https://www.npr.org/sections/health-shots/2020/05/27/862215848/across-texas-black-and-hispanic-neighborhoods-have-fewer-coronavirus-testing-sit

Other socioeconomic factors can also result in barriers to testing

Barriers	Mitigation Strategies
• Insurance status • Immigration status and fear of ICE • Distrust of government systems • Communication and language barriers • Lack of ability to safely isolate after a positive test due to employment insecurity or personal/family obligations • Fear of getting a test because of risk of losing work/income	• Universal testing paid for by government, regardless of insurance or immigration status • Eliminate police presence at testing sites and ensure no information is shared with non-health personnel • Hire test site staff directly from the community • Provide resources to support safe isolation and quarantine • Provide paid time off and sick leave for employees waiting for test results, quarantining, and isolating

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- **Outstanding questions**
- Appendix

Outstanding Questions

- How best to **balance cost of testing, turn around times, and accuracy** (e.g. PCR testing and antigen testing)?
- When is **the best time** in the course of the disease to test, and with what testing modality?
- How does **viral load** impact decision-making? Should cycle times be considered when making isolation decisions?
- How should **asymptomatic contacts** be managed? When and with what testing modality?
- Is there a benefit of **"double testing"** to improve positive and negative predictive value? I.e., when pre-test probability is high, and yet a negative result is obtained? If double testing is deployed, what is the best way to manage discordant results?
- Is **population surveillance** possible and/or practical? What role should different methods play, such as antigen tests, antibody tests, or wastewater analysis?
- What is the **role for surveillance in medium-risk vs. low-risk groups**?
- How might **innovative testing and screening approaches be scaled in the US**, such as training dogs or using AI to analyze coughs?

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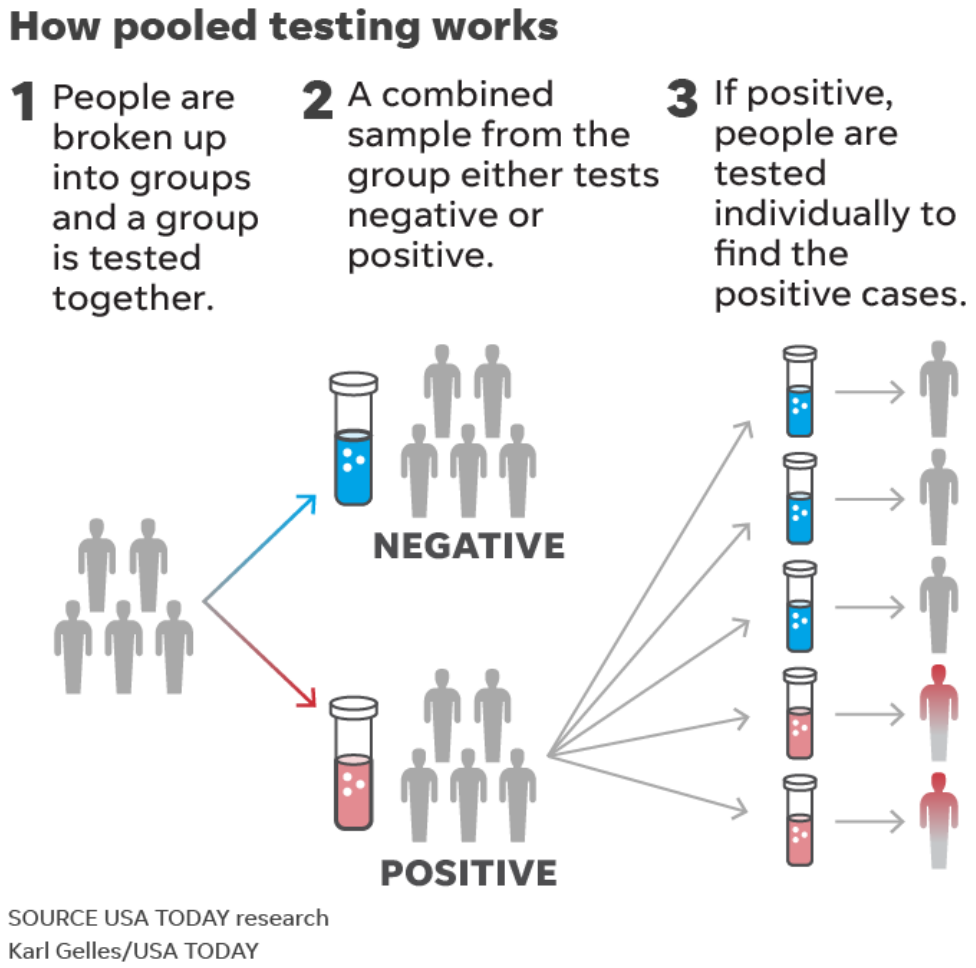
- Outstanding questions
- **Appendix**

CLIA regulations pertain to diagnostic and screening tests depending on the level of test complexity

Term	Definition	Implication
CLIA	Clinical Laboratory Improvements Amendments. CMS oversight body regulating all tests that result to a patient	Almost all testing is included except for research and forensics
CLIA – waived tests	Any laboratory test deemed by the FDA to be simple enough that there is an insignificant risk of an erroneous result. These tests are exempt from CLIA rules if following the manufacturer's instructions	Deemed so simple that they do not require licensure to conduct, interpret, or resport
CLIA certificate of waiver	A waiver obtained by a laboratory to allow conducting of testing, their interpretation, and delivery to a patient	A "laboratory" refers to any group of people if there is designated lab director. Easily obtainable
Moderate and High complexity lab tests	More complex tests that require specific regulations for persons performing and interpreting the tests with corresponding responsibilites for each position	PCR testing generally falls under this designation except for POC NAA tests
Certificate of compliance (COC) / accreditation (COA)	Denote higher levels of laboratory certification required to perform medium to high complexity lab tests	Many state and county laboratories fit this more advanced designation

Pooled testing allows for increased testing capacity in surveillance



Pooled testing is useful in populations where prevalence is expected to be low (if all pool samples test positive, no resources have been saved)

Most useful when routine, repeat testing is needed in congregate living areas such as skilled nursing facilities or dormitories[1]

School classrooms may be another opportunity to leverage pooled testing

Samples can be pooled at the point of collection or later at the lab before the test is run

In Massachusetts, a pilot is ongoing which uses a team of mobile test vans to pool and run testing for a network of nursing homes[2]

1. Dr. Kong, Stanford Health, https://med.stanford.edu/news/all-news/2020/07/stanford-health-care-can-begin-pooled-testing-for-covid-19.html
2. https://www.theatlantic.com/health/archive/2020/08/how-to-test-every-american-for-covid-19-every-day/615217/

Side-by-side Comparison of Testing Technologies

SARS-CoV-2 Testing Methods						
Component Detected	***Nucleic Acid Testing***				***Antigen Testing***	
Method	**RT-qPCR**	**Nucleic Acid Amplification**	**Genome Sequencing**	**CRISPR**	**ELISA**	**Lateral Flow Assay**
Clinical Accuracy	High	High	High	Medium	Unknown	Medium
Scalable to Meet US Needs?	Maybe	Maybe	Yes	Unknown	Unknown	Yes
Current US Tests/Day	~200,000	~5,000	0	0	0	Thousands
Projected Aug. 2020 Tests/Day	Hundreds of Thousands	Hundreds of Thousands	Millions	Unknown	Unknown	Hundreds of Thousands
Use Case	High-volume Centralized **or** Point-of -Care	High-volume Centralized **or** Point-of -Care	High-volume Centralized	Point-of-Use	High-volume Centralized	Point-of-Use
Turnaround Time	24-48 Hours (Centralized) Minutes (PoC)	24-48 Hours (Centralized) Minutes (PoC)	24–48 Hours	Minutes	24–48 Hours	Minutes
Sample Type	Nasal Swab or Saliva	Nasal Swab	Nasal Swab or Saliva	Nasal Swab	Unknown	Nasal Swab
Quantifies Viral Load	Yes	No	Yes	No	Yes	No
Key Scale-Up Barrier	Reagent/Kit Availability	Reagent/Kit Availability	Logistics	Novel Technology	Assay Development	Assay Development
Regulatory Status	EUA	EUA	EUA pending	EUA	Unknown	EUA
Supply Chain Risk	Medium	High	Low	Medium	Medium	Low
Representative Companies	LabCorp Quest Roche Thermo Fisher	Abbott Hologic Atila Bio	Broad Inst. Illumina Hudson Alpha Ginkgo	Mammoth Sherlock Broad Inst.	LabCorp Quest Abbott Roche	Quidel ChemBio Cellex OraSure

https://docs.google.com/document/d/1tDc622k8YHW2izTsTBTSR1Gf7UQuK_DtylWgOvgi36s/edit

US Public Health Accompaniment Unit

For more information please contact LearningCollab@pih.org

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