

# Evaluating the Quality and Reliability of Covid-19 Diagnostic Tests



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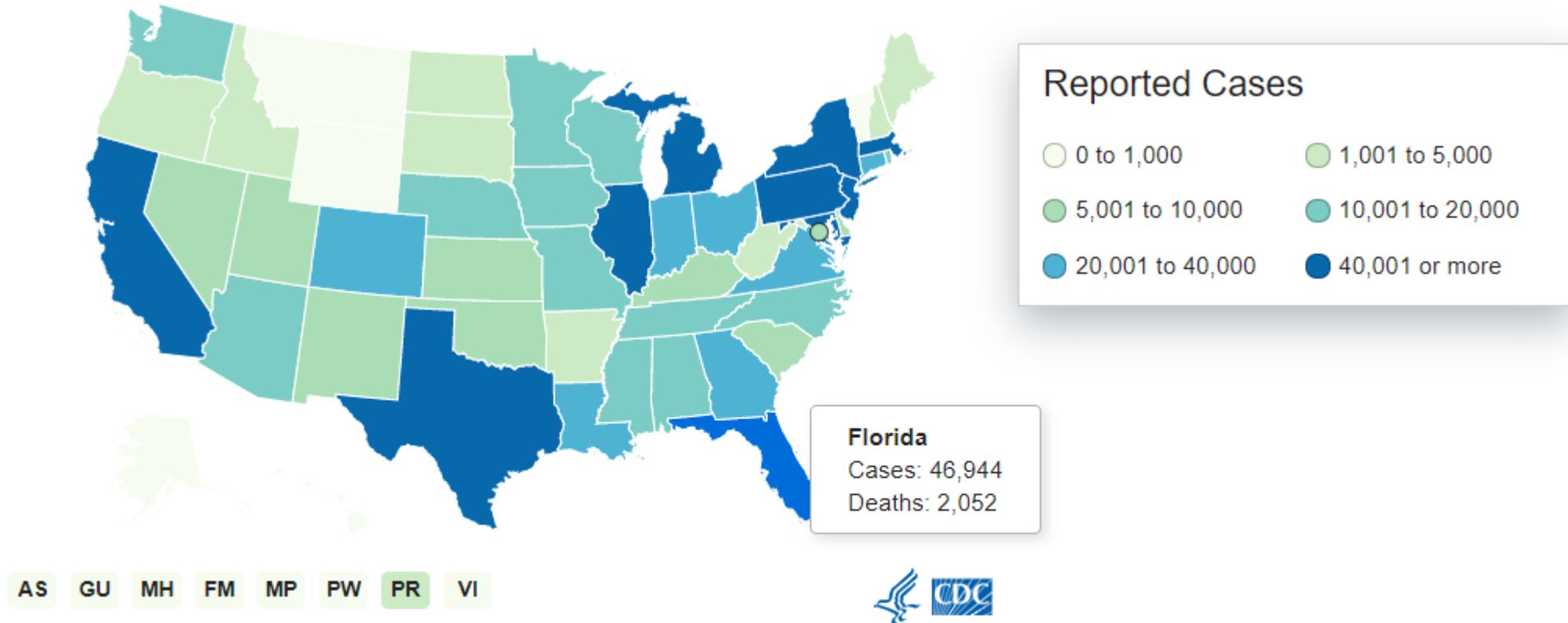


ASQ South Atlantic Region

May 21<sup>st</sup>, 2020

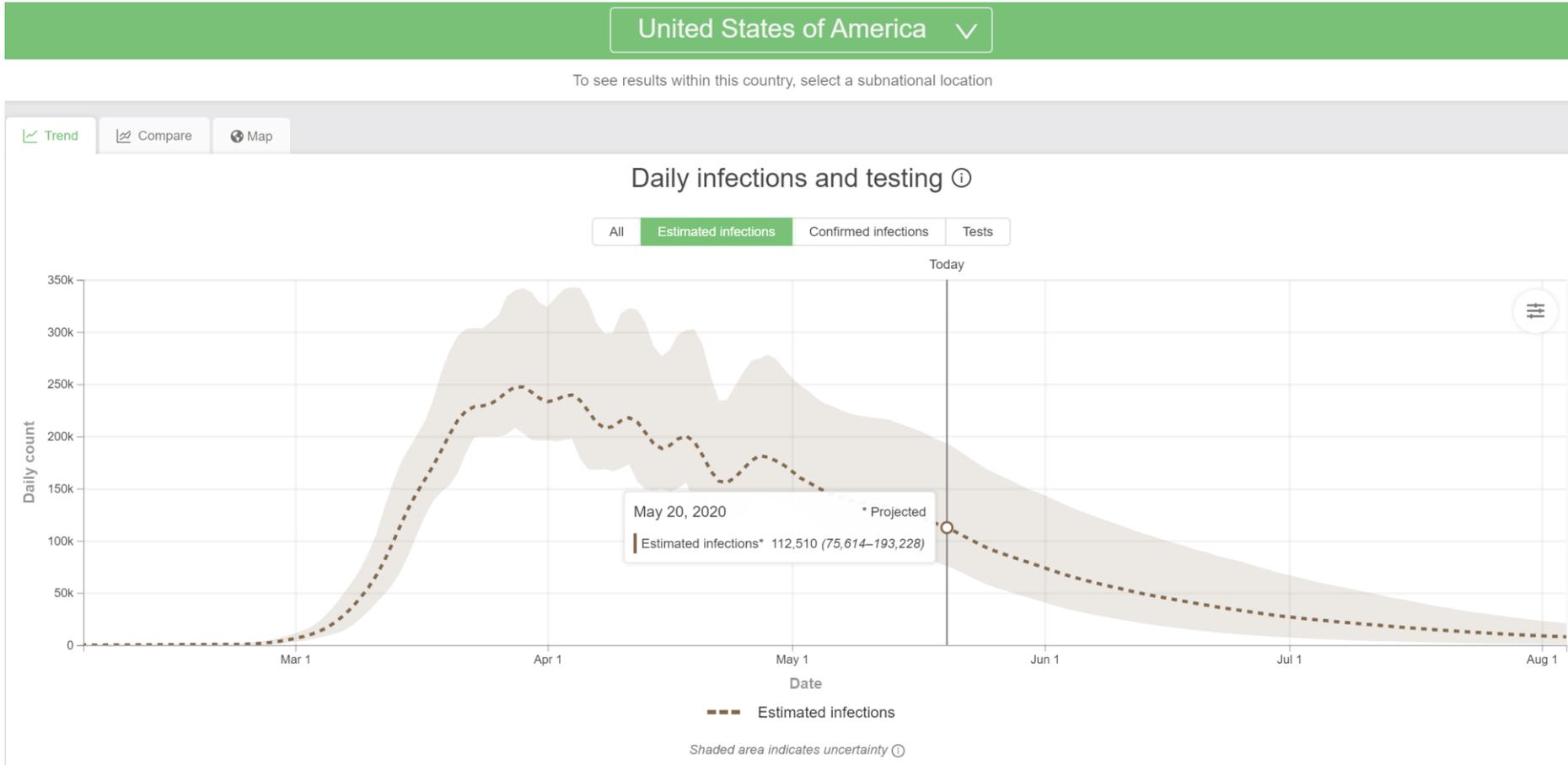
29 states report more than 10,000 cases of COVID-19.

This map shows COVID-19 cases and deaths reported by U.S. states, the District of Columbia, and other U.S.-affiliated jurisdictions. Hover over the map to see the number of cases and deaths reported in each jurisdiction. To go to a jurisdiction's health department website, click on the jurisdiction on the map.



Source: cdc.gov, data as of 21 May 2020

# Current Models Project a Lot of Uncertainty



“For estimated infections, we start with death estimates, then work backward, using infection fatality ratios to estimate infections based on deaths”.

Source: Institute for Health Metrics and Evaluation

# Doubts and Concerns Persist About Testing

FOX 35 Orlando

AdventHealth says 25,000 of its COVID-19 test results are 'unreliable'

ORLANDO, Fla. - AdventHealth says the results of more than 25,000 coronavirus tests performed by the health system in Central Florida are ...  
1 day ago



FDA U.S. FOOD & DRUG ADMINISTRATION

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FDA NEWS RELEASE

## Coronavirus (COVID-19) Update: FDA Informs Public About Possible Accuracy Concerns with Abbott ID NOW Point-of-Care Test

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Washington Post

Dozens of coronavirus antibody tests on the market were never vetted by the FDA, leading to accuracy concerns

Dozens of coronavirus antibody tests on the market were never vetted by the FDA, leading to accuracy concerns. Aggressive marketing of the ...

In-Depth · 1 month ago

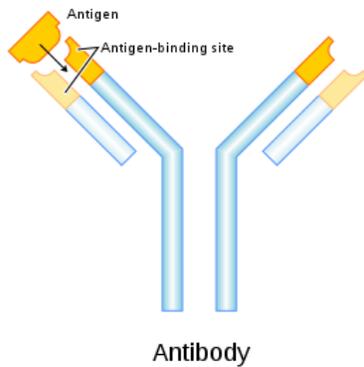
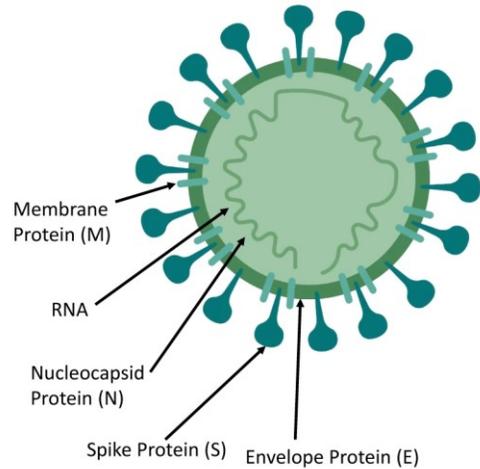


Sources: various news outlets

# Topics for Today

- ❑ **Overview of Different Types of Testing**
- ❑ **Focus on Antibody Testing**
  - ELISA and Lateral Flow Techniques
  - Understanding Accuracy
  - Understanding “Real World” Performance
  - Current Performance Levels of FDA Authorized Tests
- ❑ **Testing in Perspective**
  - Individual vs. Public Health Considerations
- ❑ **Discussion**
  - How can Quality Professionals help?
  - Q&A

# 3 Types of Tests for SARS-CoV2



## RT-PCR Tests

- Detect Viral RNA
- High Sensitivity & Specificity
- Slow, Limited Point of Care



## Antigen Tests

- Detect Viral Proteins (S, M or N)
- Medium Sensitivity & Specificity
- Rapid Results, Point of Care



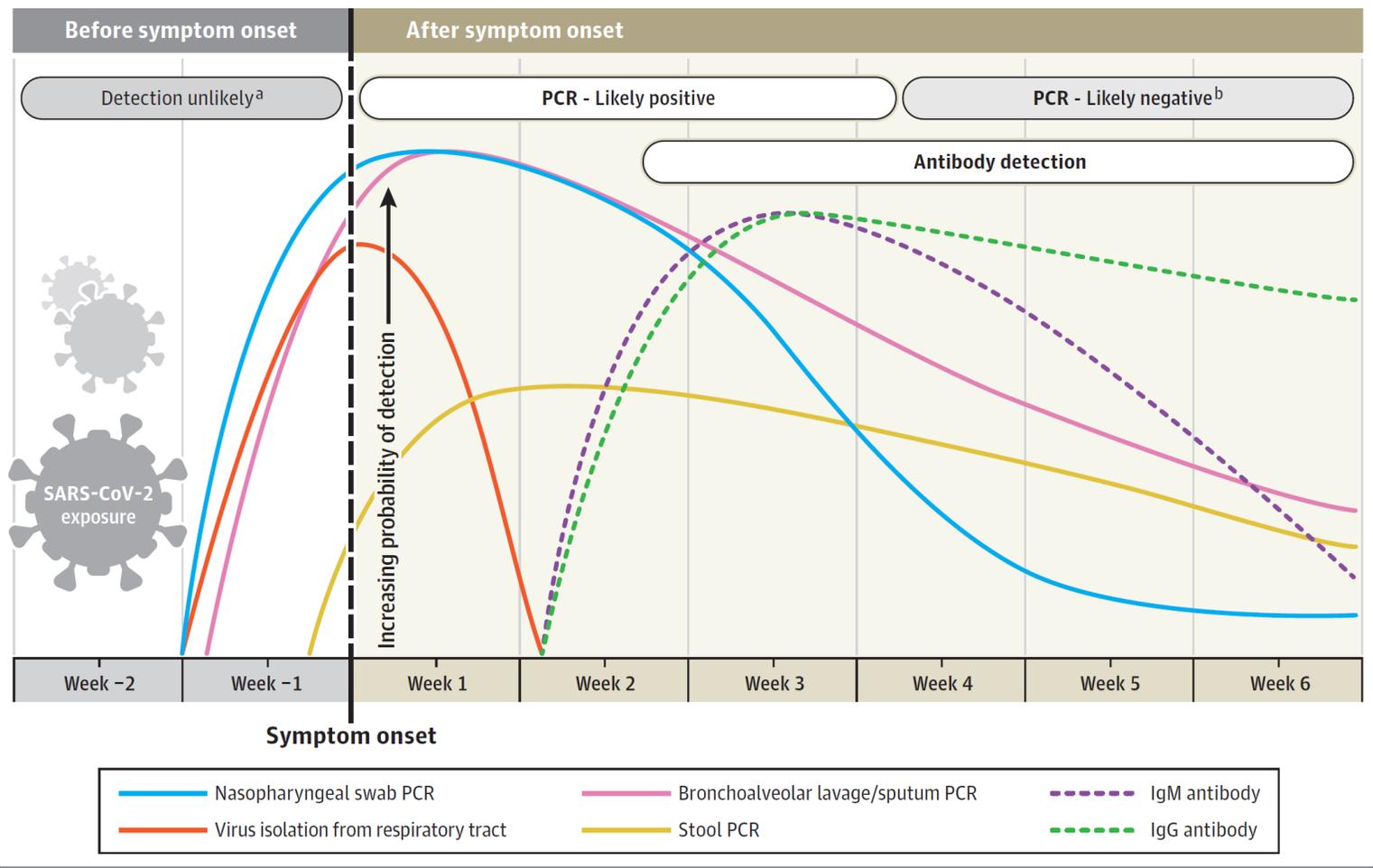
## Antibody Tests

- Detect antibodies
- Medium Sensitivity & Specificity
- Rapid Results, Point of Care



Image Credits: Nature, Wikipedia and Company Websites  
For illustration only, no affiliation with specific tests

# When You Test Matters



Source: "Interpreting Diagnostic Tests for SARS-CoV-2", JAMA, 6 May 2020

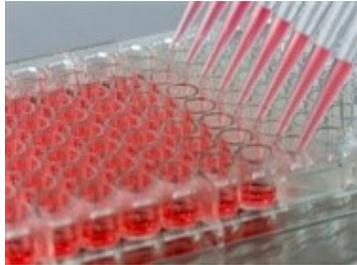
# A Quick Overview of Two Techniques

## 1 ELISA – Enzyme Linked ImmunoSorbent Assays

Microtiter plate coated with SARS-CoV2 recombinant binding domain protein (RBD)



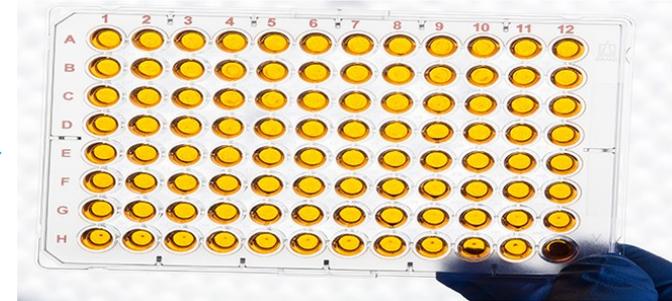
Load diluted sample



Wash and add secondary anti-human IgG HRP



Add substrate  
Color change => positive



Note: There are many more steps involved and a second confirmatory, more quantitative test is done for presumed positive samples

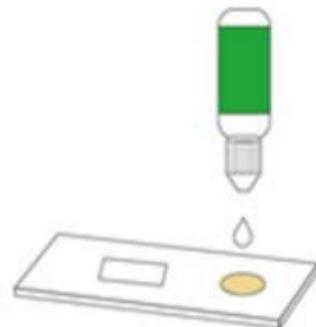
# A Quick Overview of Two Techniques

2

## Lateral Flow Immunoassay

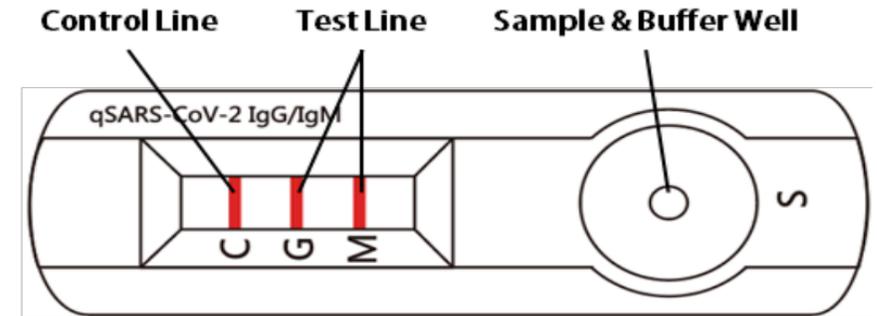


10µL sample



2 drops of  
sample diluent

15-20 min



Only C -> negative

C and M -> IgM Positive

C and G -> IgG Positive

C, M and G -> IgM and IgG Positive

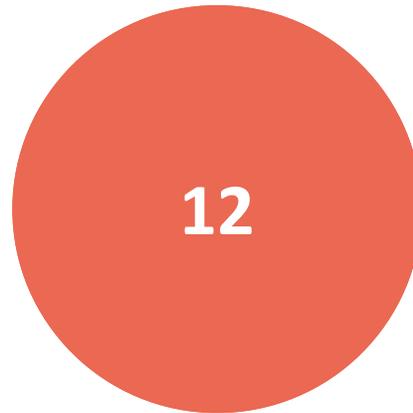
Source: Cellex q Rapid Test IFU

# More than 100 Tests Authorized by the FDA

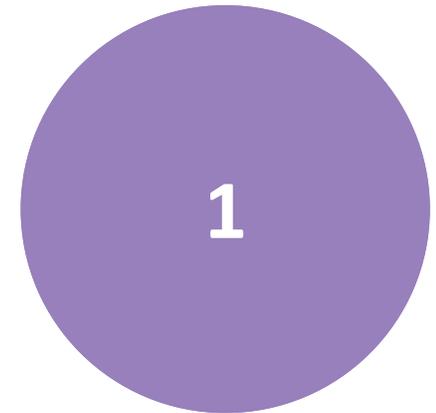
## RT-PCR Tests



## Antibody Tests



## Antigen Tests



Source: FDA Emergency Use Authorizations  
Count as of May 20, 2020, RT-PCR count includes Lab Developed Tests (LDT)

# Understanding Test Accuracy

	Infected	Uninfected
Has Antibodies	True Positive	False Positive
Does Not Have Antibodies	False Negative	True Negative

# Estimating Test Accuracy – Lab Validation

	Infected	Uninfected
Has Antibodies	TP 27	FP 4
Does Not Have Antibodies	FN 3	TN 76

**Diagnostic Sensitivity,  $DS_n$**   
 $27/30 = 90\%$   
95% CI = **73.5% - 97.9%**

**Diagnostic Specificity,  $DS_p$**   
 $76/80 = 95\%$   
95% CI = **87.7% - 98.6%**

For illustration only; based on recently announced FDA expectations for IgM/IgG serology tests

# What Does This Mean in the Real World?



Say you got a **positive** result and you ask your doctor – “Are you sure I have the antibodies to SARS-CoV-2?”

Or, say you got a **negative** result and you ask your doctor – “Are you sure I don't have the antibodies to SARS-CoV-2?”

Note – none of the current antibody tests are authorized for use at home



# We Need to Know the Predictive Value of a Test

## Positive Predictive Value (PPV)

Given a positive result, what is the likelihood that the individual has antibodies to SARS-CoV-2?

## Negative Predictive Value (NPV)

Given a negative result, what is the likelihood that the individual does not have antibodies to SARS-CoV-2?

Note – An alternate approach is to use Likelihood Ratios

# So, How Well Does a Test Perform in Real Life?

Diagnostic Sensitivity,  $DS_n = 90\%$

Diagnostic Specificity,  $DS_p = 95\%$

	PPV	NPV
5% Prevalence	49%	99%
25% Prevalence	86%	97%

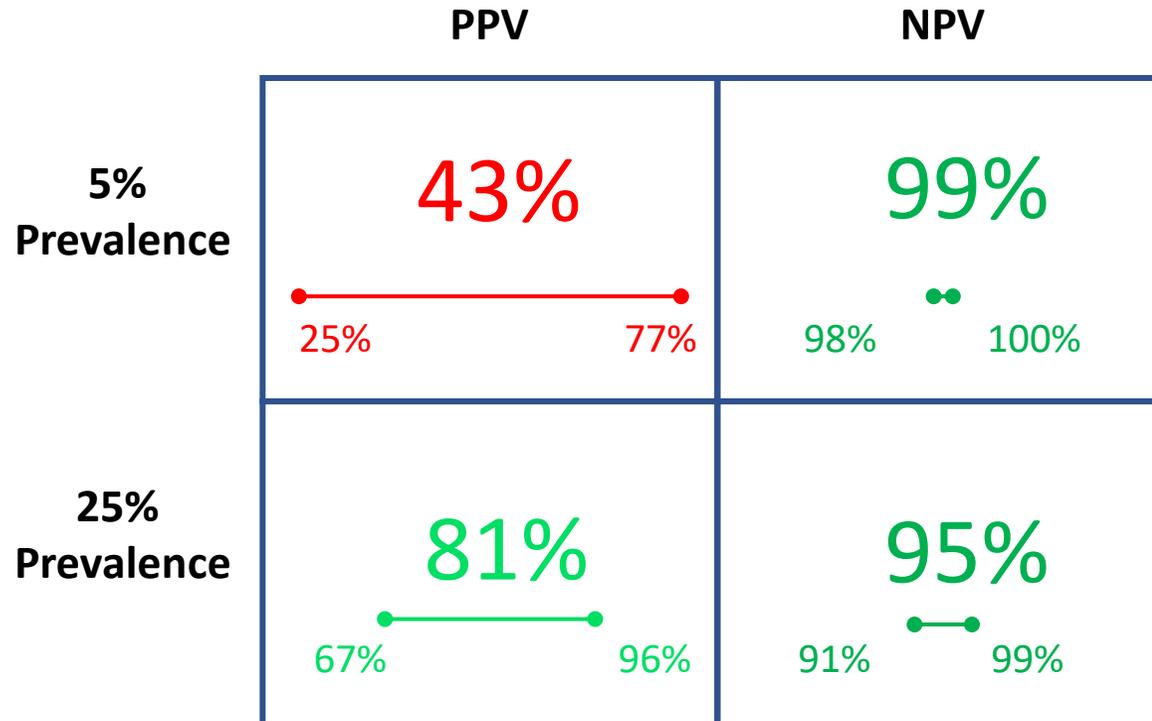
# But Wait...Recall the 95% Confidence Interval?

Diagnostic Sensitivity,  $DS_n = 90\%$

95% CI = 73.5% - 97.9%

Diagnostic Specificity,  $DS_p = 95\%$

95% CI = 87.7% - 98.6%



# Should We Increase $DS_n$ or $DS_p$ ?

Scenario 1:

$DS_n = 95\%$

$DS_p = 95\%$

	PPV	NPV
5% Prevalence	50%	100%
25% Prevalence	86%	98%

# Should We Increase $DS_n$ or $DS_p$ ?

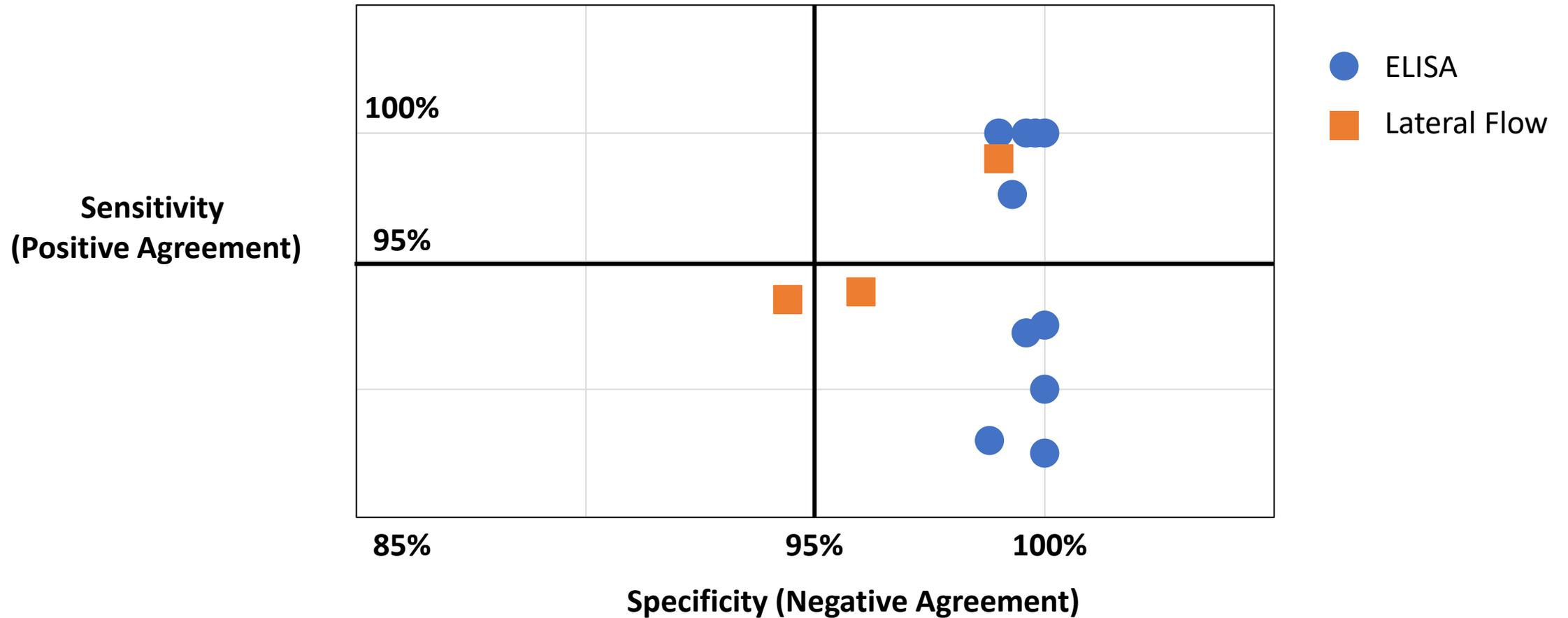
Scenario 2:

$DS_n = 90\%$

$DS_p = 99\%$

	PPV	NPV
5% Prevalence	83%	100%
25% Prevalence	97%	97%

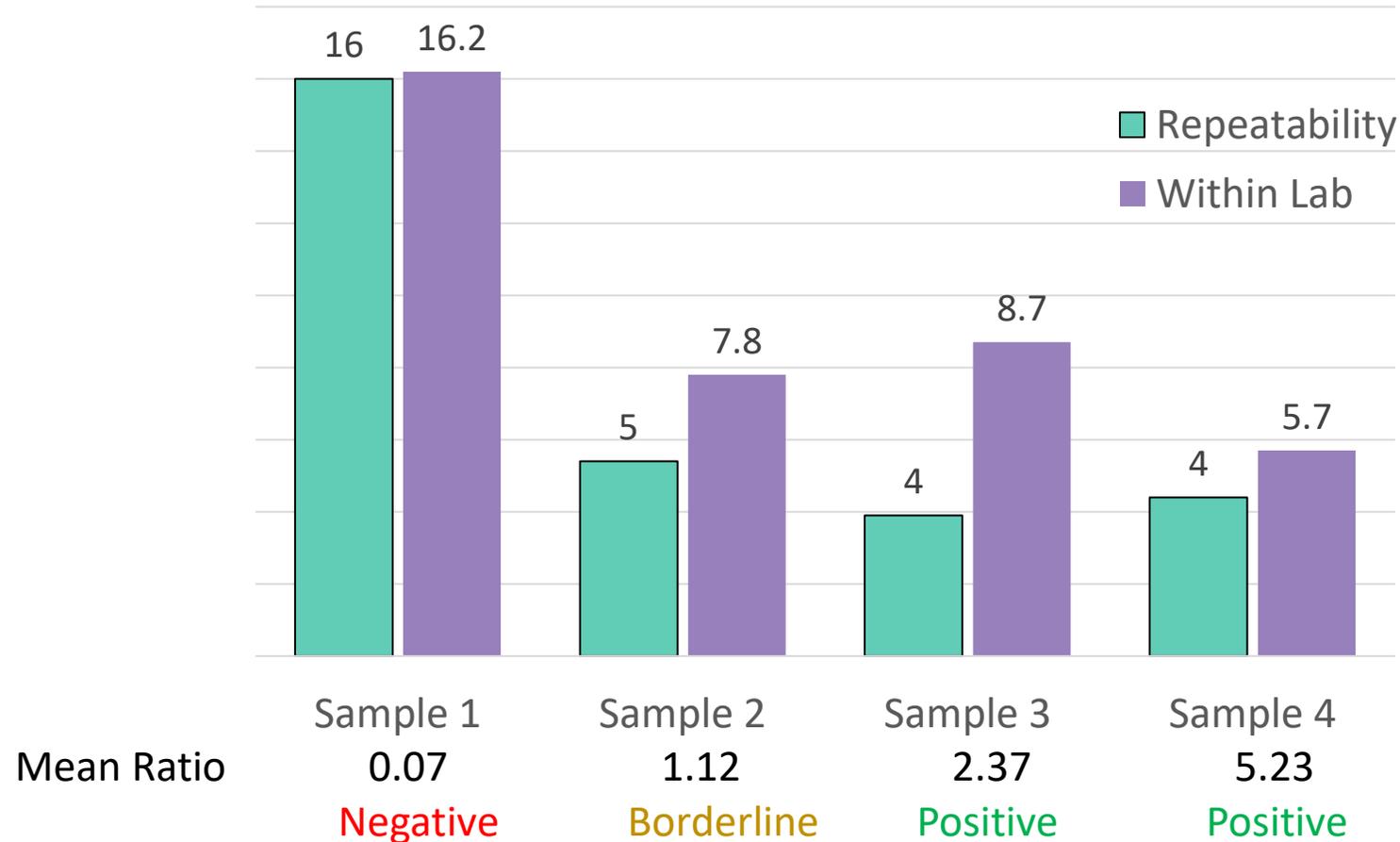
# Lab Performance of FDA Authorized Tests



Data Source: EUA Authorized Serology Test Performance  
<https://www.fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-test-performance>

# Limited Data Availability on Precision

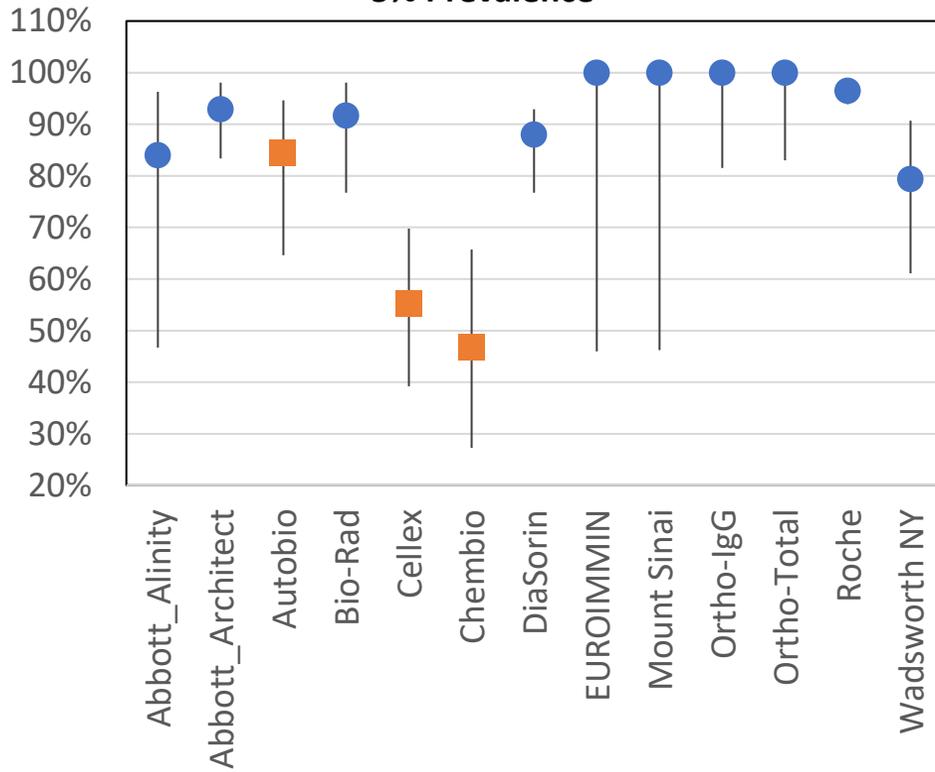
## Reported %Coefficient of Variation for an ELISA Antibody Test



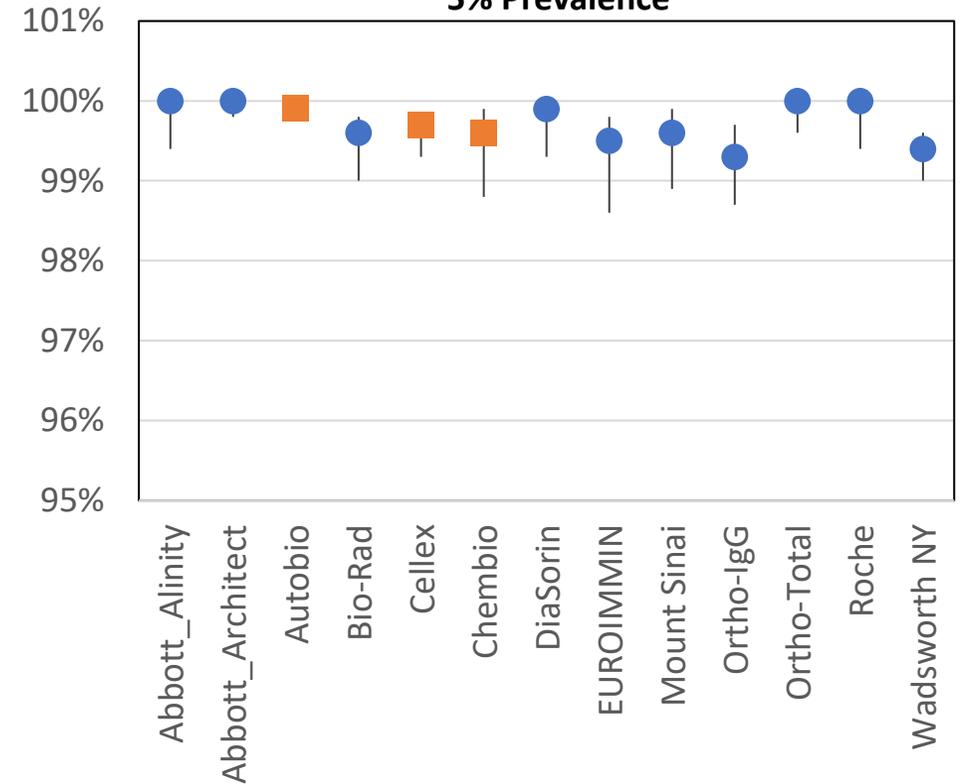
Data Source: Instruction for Use <https://www.fda.gov/media/137609/download>

# Expected Real-World Test Performance

**Positive Predictive Value (PPV)**  
5% Prevalence



**Negative Predictive Value (NPV)**  
5% Prevalence



● ELISA    ■ Lateral Flow

Source: FDA website  
<https://www.fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-test-performance>

# FDA Has Now Established Minimum Requirements

## Independent Validation of the Covid-19 Serology Test



	Positive Agreement	Negative Agreement
<b>Sample Type</b>	Serum/Plasma	Serum/Plasma
<b># of Samples</b>	30 Confirmed Positive	80 Confirmed Negative Or Pre-Covid19 10 must be HIV Positive
<b>Requirement</b>	Combined – 90% Pos. Agreement IgM – 70% Positive Agreement IgG – 90% Positive Agreement	Combined – 95% Neg. Agreement No cross reactivity with HIV

Source: FDA Letter of Authorization <https://www.fda.gov/media/137470/download>

# Emerging FDA Priorities for Testing



Saliva based tests

At-home collection and testing

Rapid Point-of-Care testing

More antigen tests

More options for swabs – 3D printing etc.

Source: FDA Virtual Town Hall Meetings

# Let Us Put This in Perspective

## Individual Level Concerns



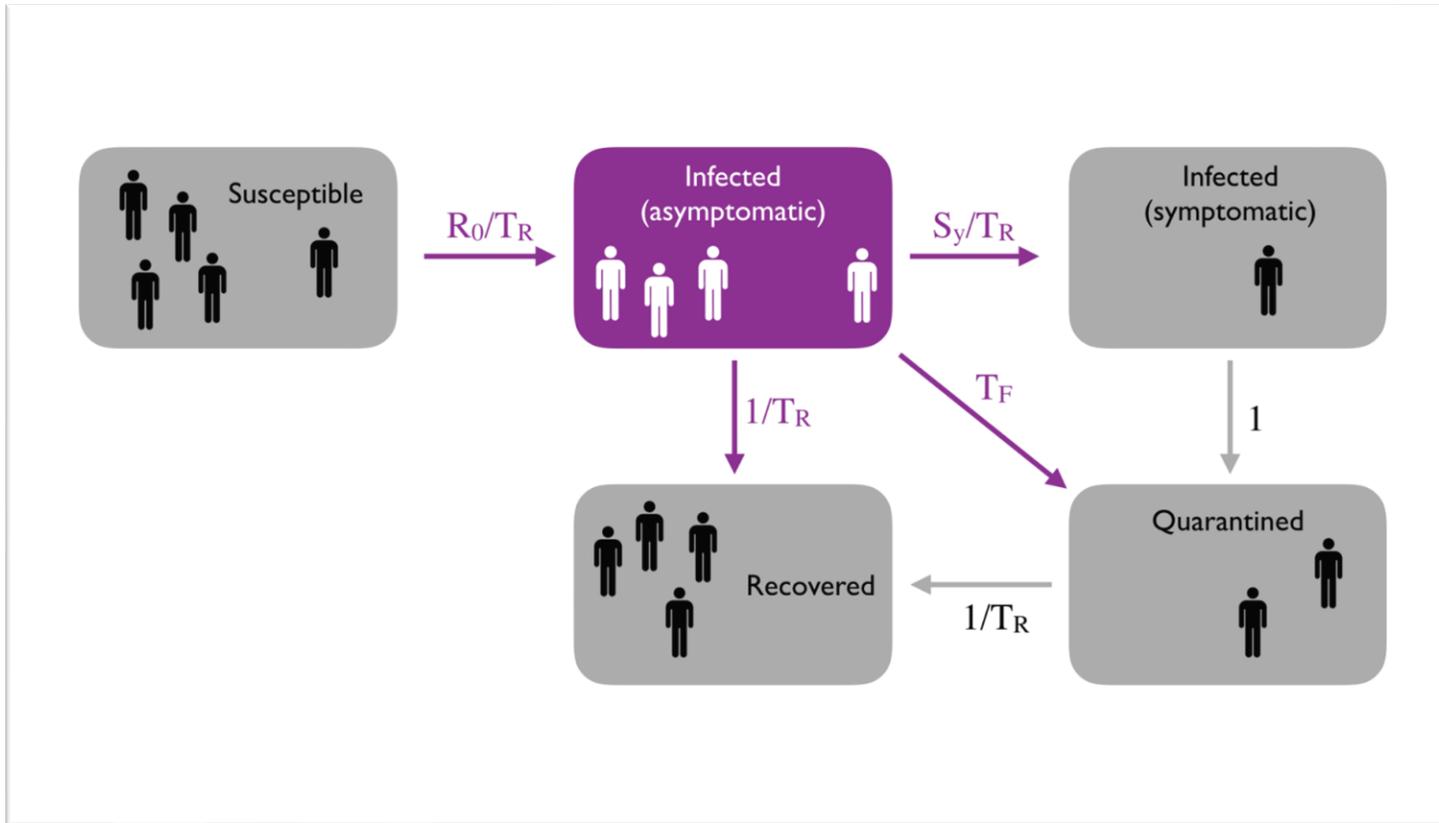
**Do I have the virus?**

**I have some symptoms – is it flu or Covid-19?**

**I have fully recovered, am I safe now?**

# Public Health Considerations

## Balancing Social Distancing with Opening Up



$R_0$  # Infected by one person

$S_y$  # Symptomatic

$T_F$  # Tested Positive

$T_R$  Days of Recovery

$$\frac{R_0 / T_R}{T_F} \leq 1$$

Detecting  $T_F$  allows us to tolerate a higher  $R_0$  because we can test, trace and isolate

Source: IDSS, MIT Institute for Data, Systems and Society

# Large Scale Population Studies on the Way



National Institutes of Health  
*Turning Discovery Into Health*



Centers for Disease Control and Prevention  
CDC 24/7: Saving Lives, Protecting People™

## National Sero-survey, April 2020

- Recruiting 10,000 volunteers nationwide
- At-home blood sample collection or at NIH
- ELISA testing, both IgM and IgG
- ClinicalTrials.Gov Identifier NCT04334954

## Multiple Seroprevalence Surveys

- Large Scale: Focusing first on WA, NY and later across the United States
- Community Level: County level sampling
- Special Population: Healthcare workers etc.

Source: NIH, CDC websites

# How Quality Professionals can Help



**Ignore sensational headlines**

**Clearly understand benefit/risk of any action**

**Help develop effective protocols and actionable metrics**

**Monitor, control and build confidence**

**Be sensitive to individual concerns**

# In Closing....

- ❑ Current Covid-19 pandemic has impacted all aspects of life
- ❑ More than 100 tests have been authorized by the FDA for emergency use
- ❑ RT-PCR, Antigen and Antibody tests offer different options across the infection lifecycle
- ❑ Testing is only one part of the overall strategy
- ❑ Quality professionals can make a significant contribution to their organizations and society at large

**We are all in this together!**



**We can do it!**

# About Exeed™

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2019 is here, and is already beginning to fly by. I invite you to check out the latest industry news in less than 15 minutes. Please let me know if there are future topics you would like discussed by [contacting me here](#).



- Naveen Agarwal, Ph.D

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FEATURE ARTICLE

**When Compliance Leaves the Customer Stranded**



A paper form that needs to be completed before the plane can leave the gate triggers a sequence of events leading to the flight cancellation.

**The Question: Are you stuck with procedures that don't make sense?**  
[Read More >>>](#)

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REGULATORY NEWS

**FDA Wants You to Take a STeP in the Right Direction**

The STeP program offers MedTech companies a clear incentive to focus their innovation efforts on improving patient safety. If their device can claim better safety outcomes, not only do they get faster approval, they can also gain a significant competitive advantage in the market.



**The question: Innovating to improve Product Safety can help you gain competitive advantage.**