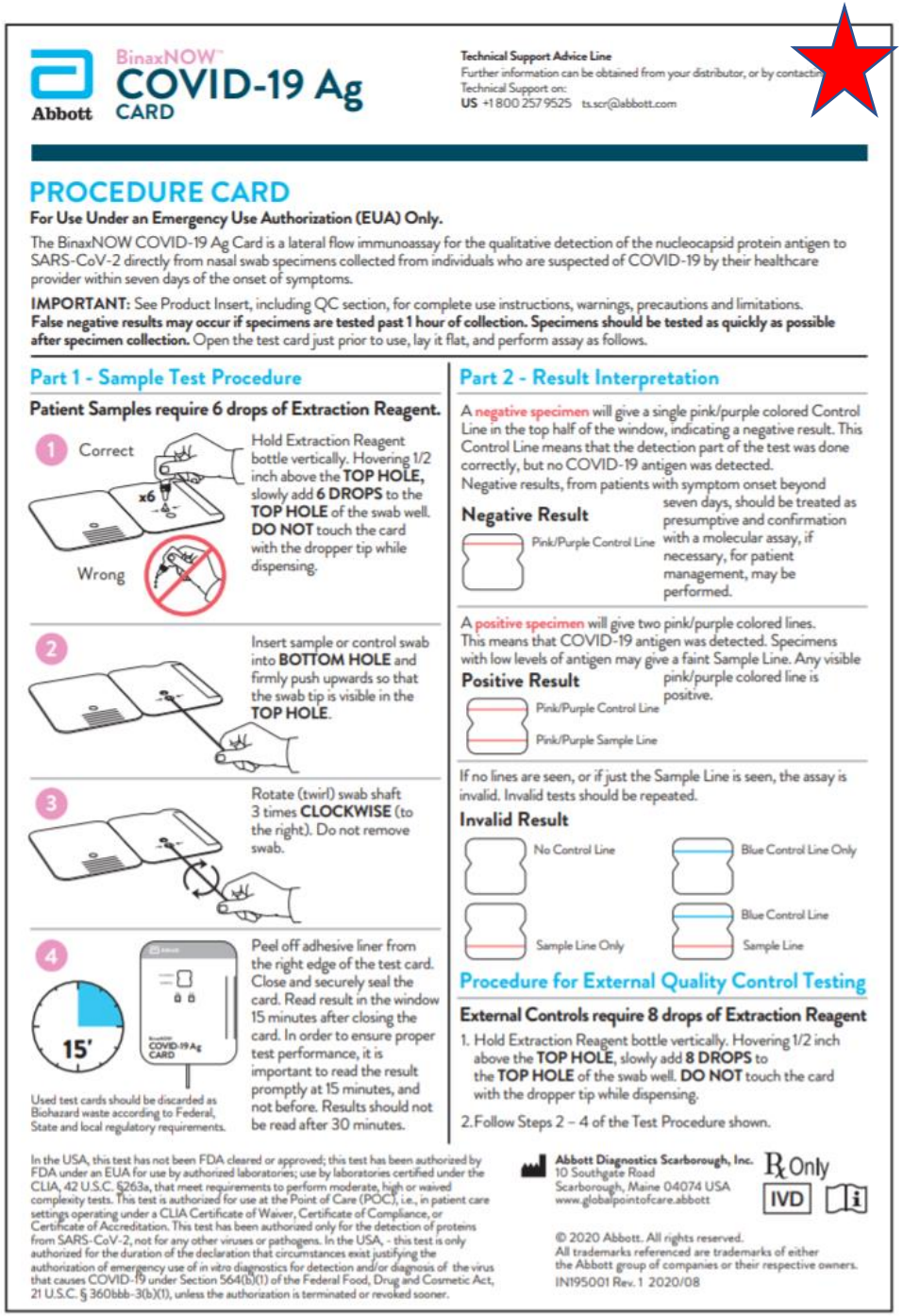

Abbott BinaxNOW™ COVID-19 Ag CARD

Technical Support Advice Line
Further information can be obtained from your distributor, or by contacting Technical Support on:
US +1 800 257 9525 ts.scr@abbott.com

PROCEDURE CARD

For Use Under an Emergency Use Authorization (EUA) Only.

The BinaxNOW COVID-19 Ag Card is a lateral flow immunoassay for the qualitative detection of the nucleocapsid protein antigen to SARS-CoV-2 directly from nasal swab specimens collected from individuals who are suspected of COVID-19 by their healthcare provider within seven days of the onset of symptoms.

IMPORTANT: See Product Insert, including QC section, for complete use instructions, warnings, precautions and limitations. **False negative results may occur if specimens are tested past 1 hour of collection. Specimens should be tested as quickly as possible after specimen collection.** Open the test card just prior to use, lay it flat, and perform assay as follows.

Part 1 - Sample Test Procedure

Patient Samples require 6 drops of Extraction Reagent.

1 Correct — Hold Extraction Reagent bottle vertically. Hovering 1/2 inch above the **TOP HOLE**, slowly add **6 DROPS** to the **TOP HOLE** of the swab well. **DO NOT** touch the card with the dropper tip while dispensing.

Wrong

2 Insert sample or control swab into **BOTTOM HOLE** and firmly push upwards so that the swab tip is visible in the **TOP HOLE**.

3 Rotate (twirl) swab shaft 3 times **CLOCKWISE** (to the right). Do not remove swab.

4 15' — Peel off adhesive liner from the right edge of the test card. Close and securely seal the card. Read result in the window 15 minutes after closing the card. In order to ensure proper test performance, it is important to read the result promptly at 15 minutes, and not before. Results should not be read after 30 minutes.

Used test cards should be discarded as Biohazard waste according to Federal, State and local regulatory requirements.

Part 2 - Result Interpretation

A negative specimen will give a single pink/purple colored Control Line in the top half of the window, indicating a negative result. This Control Line means that the detection part of the test was done correctly, but no COVID-19 antigen was detected. Negative results, from patients with symptom onset beyond seven days, should be treated as presumptive and confirmation with a molecular assay, if necessary, for patient management, may be performed.

Negative Result

Pink/Purple Control Line

A positive specimen will give two pink/purple colored lines. This means that COVID-19 antigen was detected. Specimens with low levels of antigen may give a faint Sample Line. Any visible pink/purple colored line is positive.

Positive Result

Pink/Purple Control Line
Pink/Purple Sample Line

If no lines are seen, or if just the Sample Line is seen, the assay is invalid. Invalid tests should be repeated.

Invalid Result

No Control Line
Blue Control Line Only
Sample Line Only
Blue Control Line
Sample Line

Procedure for External Quality Control Testing

External Controls require 8 drops of Extraction Reagent

1. Hold Extraction Reagent bottle vertically. Hovering 1/2 inch above the **TOP HOLE**, slowly add **8 DROPS** to the **TOP HOLE** of the swab well. **DO NOT** touch the card with the dropper tip while dispensing.
2. Follow Steps 2 – 4 of the Test Procedure shown.

In the USA, this test has not been FDA cleared or approved; this test has been authorized by FDA under an EUA for use by authorized laboratories; use by laboratories certified under the CLIA, 42 U.S.C. §263a, that meet requirements to perform moderate, high or waived complexity tests. This test is authorized for use at the Point of Care (POC), i.e., in patient care settings operating under a CLIA Certificate of Waiver, Certificate of Compliance, or Certificate of Accreditation. This test has been authorized only for the detection of proteins from SARS-CoV-2, not for any other viruses or pathogens. In the USA, - this test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of *in vitro* diagnostics for detection and/or diagnosis of the virus that causes COVID-19 under Section 564(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Abbott Diagnostics Scarborough, Inc.
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Scarborough, Maine 04074 USA
www.globalpointofcare.abbott

℞ Only IVD

IN195001 Rev. 1 2020/08

COVID-19 Science Communications: Antigen Testing

October 28, 2020

S. Todd Stolp MD

1. Most slides are designed for LHOs, professional colleagues, health workers and LHD staff
2. Slides marked with a star in the upper left are deemed suitable for members of the general public.

These materials are current according to the dates noted and are subject to change according to the rapidly evolving study of COVID-19.

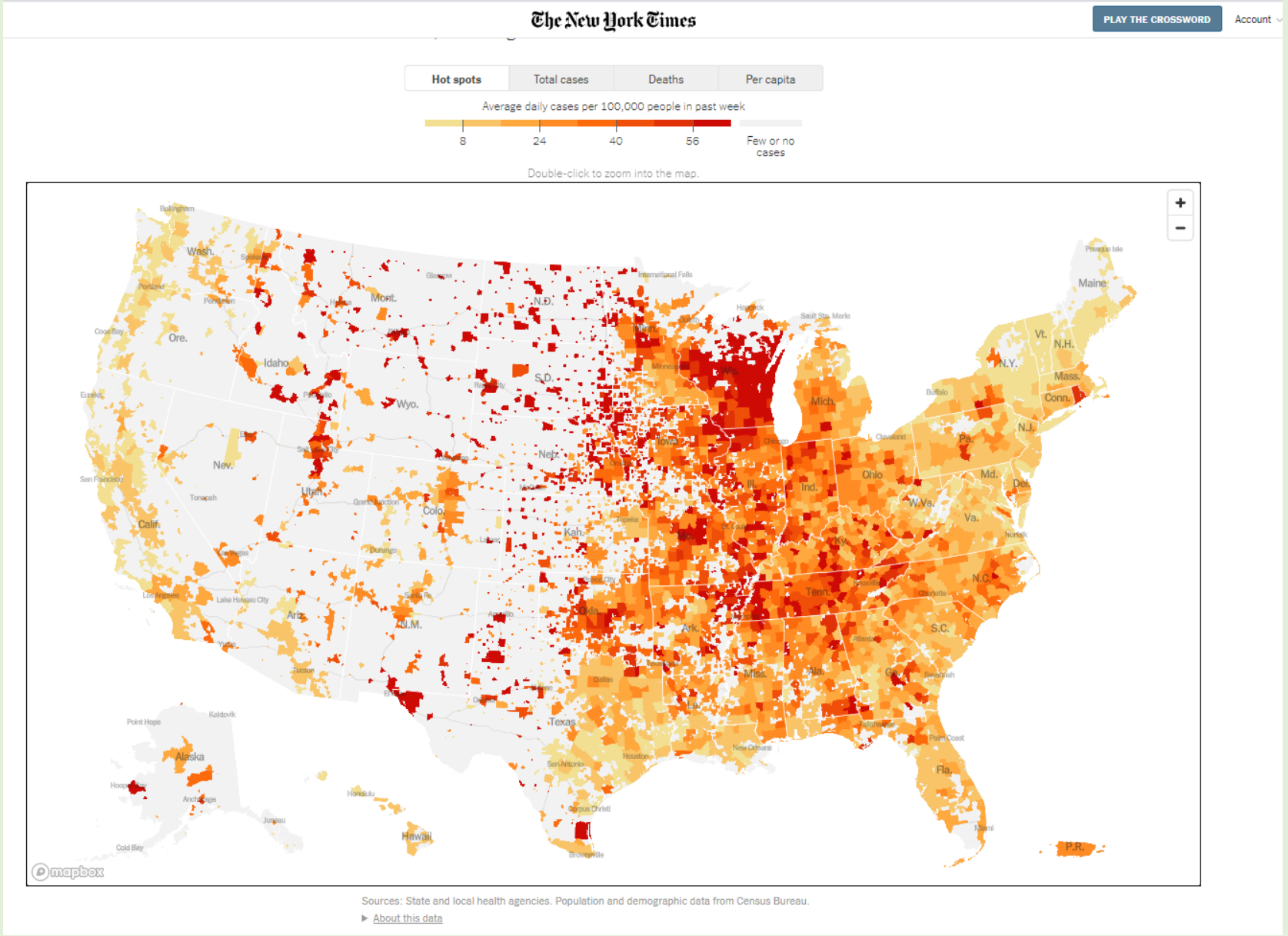
Proposed Talking Points for the **Public** on COVID-19 Antigen Testing

1. Gaining further control over the COVID-19 outbreak will require targeted testing of possible cases in our community, particularly focusing on high risk group settings like skilled nursing facilities, schools, homeless communities and prisons, and utilizing lab tests that have a rapid turnaround so the results can contribute to good clinical and public health decisions.
2. In the coming months, Health Departments across in California and across the country will be working with local partners and residents to distribute new COVID-19 Tests with guidance specific to their communities to maximize the benefit of using these tests to contain and control the COVID-19 outbreak.
3. In the meantime, it remains important to continue your diligence in combatting this pandemic and helping to protect community members by wearing masks, physical distancing, staying home when ill, hand washing and practicing good hygiene.

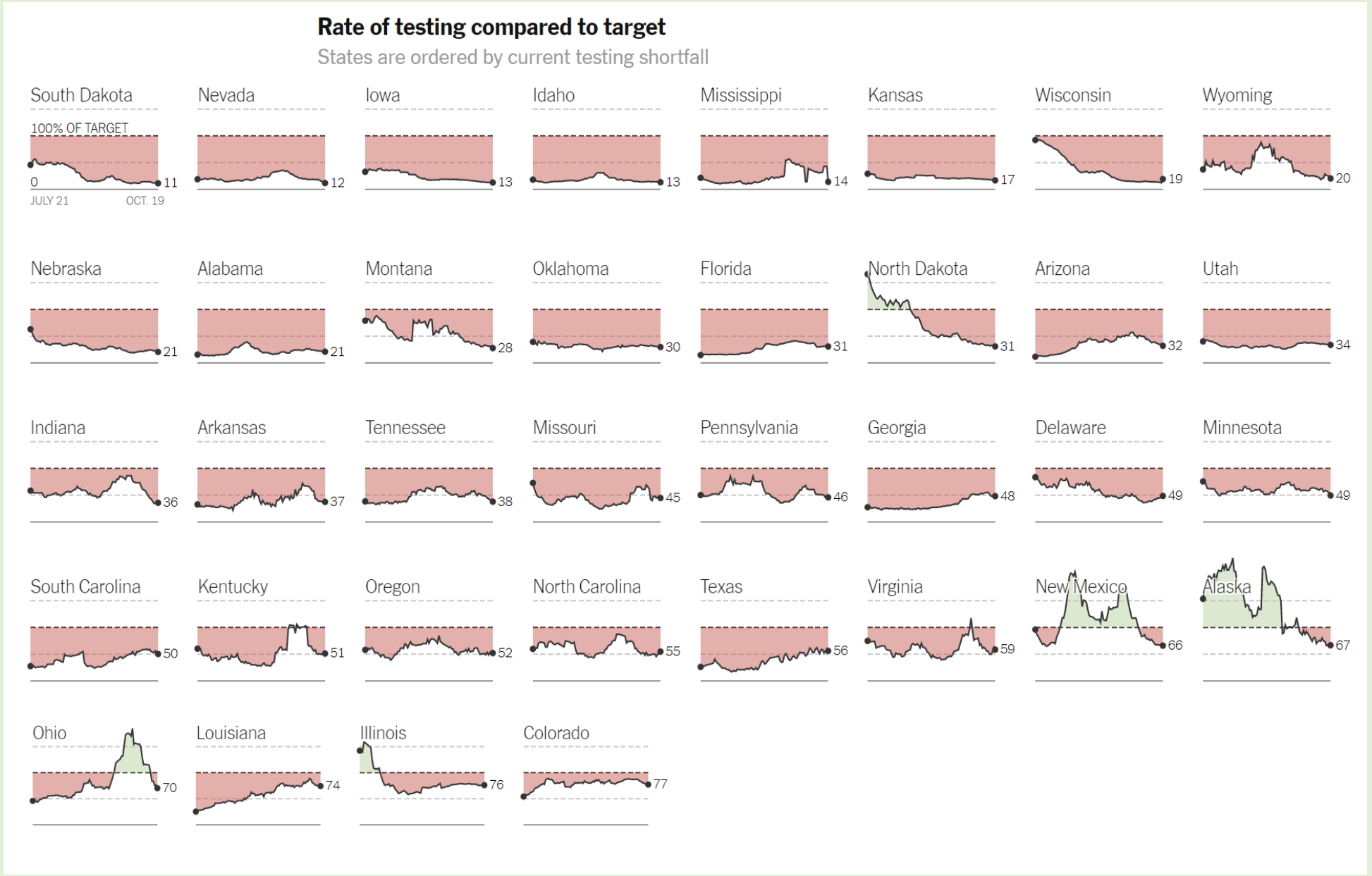
Additional Talking Points for **Health Care Partners** on COVID-19 Antigen Testing

1. Evaluating the results of a rapid antigen test for COVID-19 should take into account the known performance accuracy of the test, instructions for use of the FDA-authorized test, the prevalence of COVID-19 in the particular community in question (number of cases in the given population over the previous 7-10 days), and the clinical symptoms and condition of the person who has been tested.

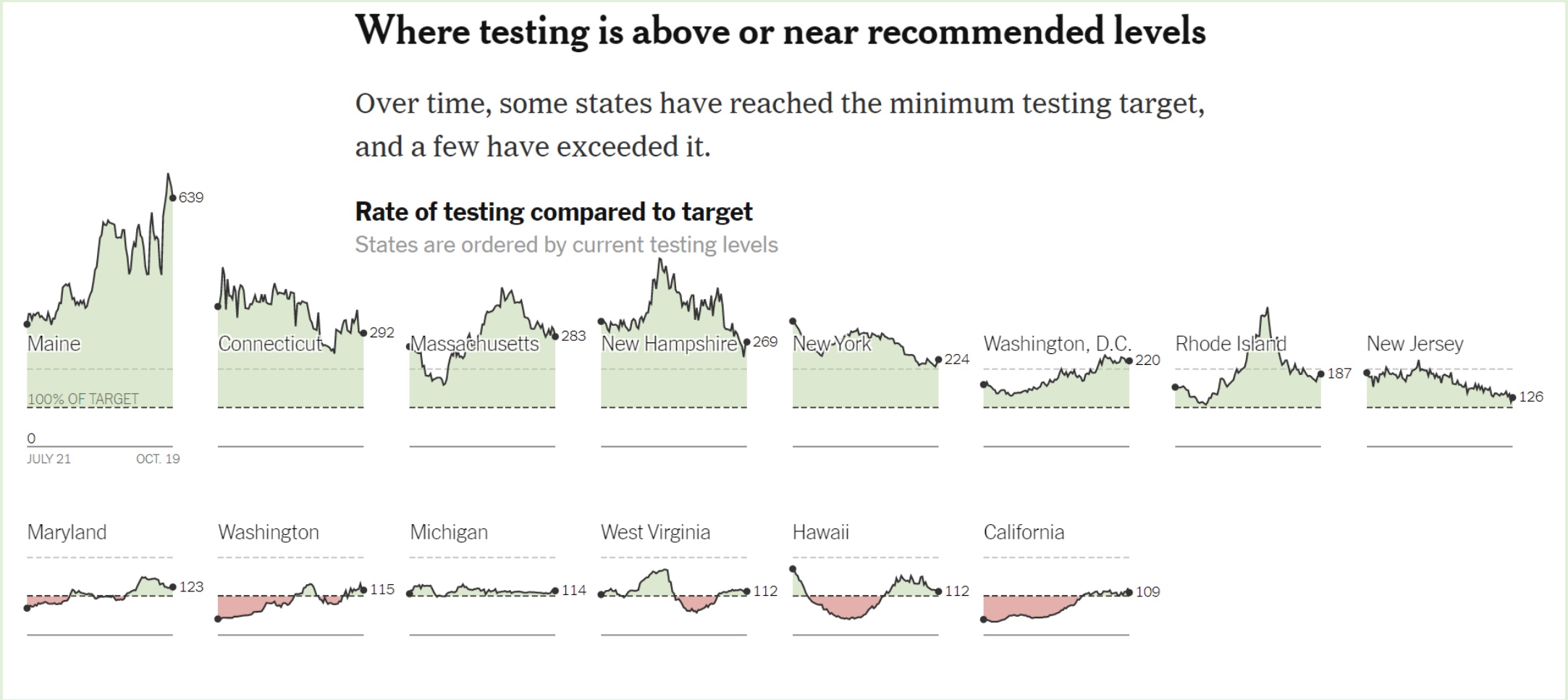
A Quick Look at COVID-19 Prevalence Relative to Testing



https://www.nytimes.com/interactive/2020/us/coronavirus-us-cases.html October 27, 2020



https://www.nytimes.com/interactive/2020/us/coronavirus-us-cases.html October 20, 2020



https://www.nytimes.com/interactive/2020/us/coronavirus-us-cases.html October 20, 2020

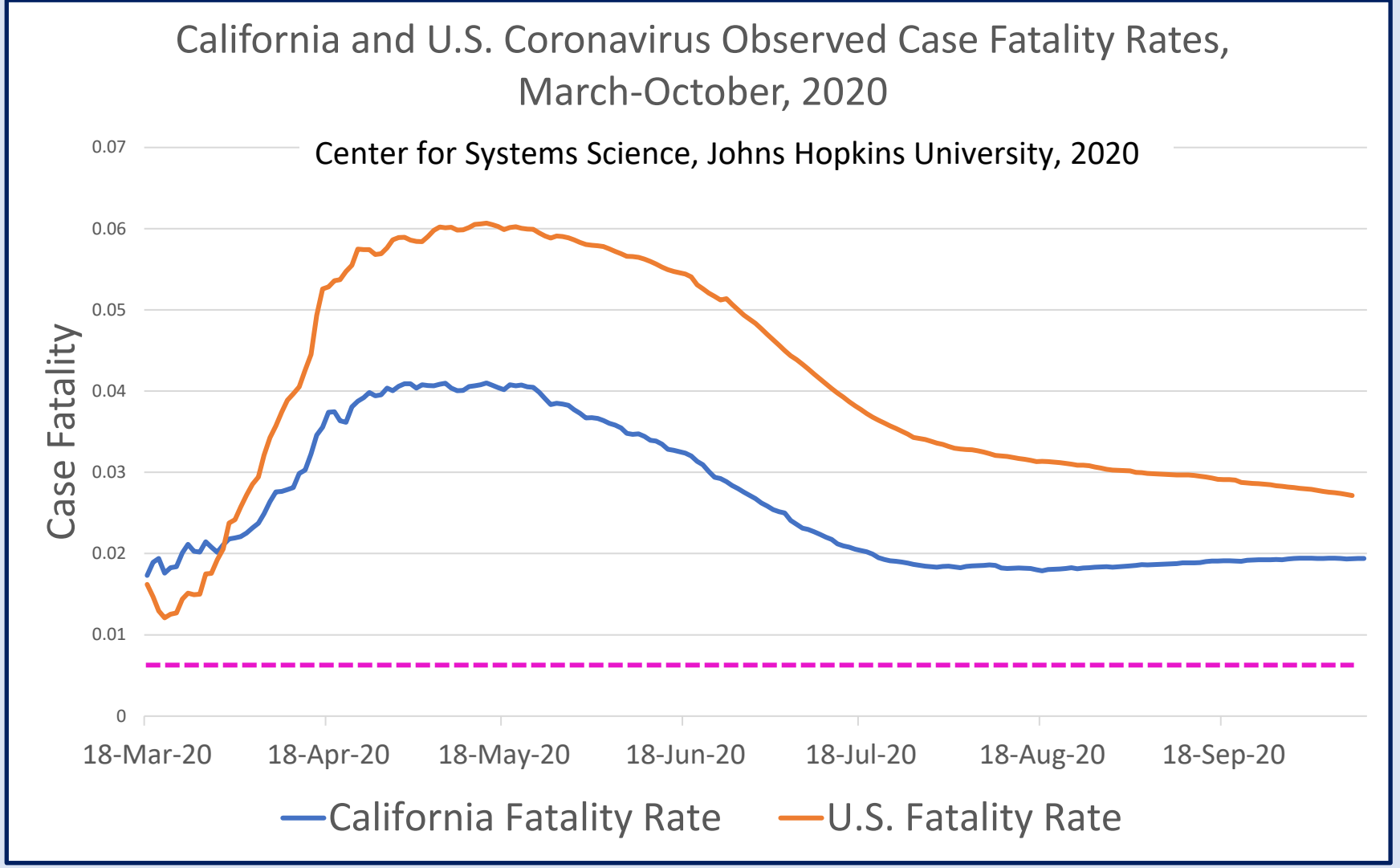


Chart compiled over the timeline indicated using daily Johns Hopkins Univ. Center for Systems Science and Engineering data posted on https://www.npr.org/sections/health-shots/2020/09/01/816707182/map-tracking-the-spread-of-the-coronavirus-in-the-u-s

During the COVID-19 outbreak, changes in the Observed Case Fatality Rate are expected to occur for a number of reasons. One important reason is the number of tests being conducted that identify asymptomatic, pre-symptomatic or minimally symptomatic infection. As testing of the population improves, the denominator increases (more cases are found) and the case fatality ratio decreases, thus more closely approximating the Infection Fatality Rate (the TRUE rate of death in people with COVID-19) which (according to cruise ship data and other studies) is estimated by the pink dotted line for the total population.

Interim Guidance for Rapid Antigen Testing for SARS-CoV-2: Definitions

Diagnostic testing for SARS-CoV-2 is intended 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.

Screening testing for SARS-CoV-2 is intended to identify infected persons who are asymptomatic and without known or suspected exposure to SARS-CoV-2 and is performed to identify persons who may be contagious so that measures can be taken to prevent further transmission. Examples include long term care facilities, camps, correctional facilities, or schools testing students, faculty and/or staff.

Surveillance testing for SARS-CoV-2 is intended to monitor for community- or population-level infection and disease, or to characterize the incidence and prevalence of disease.

https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html Last updated September 4, 2020

Implications for the different categories of testing for SARS-CoV-2: Pretest Probability

Diagnostic testing: The presence of risk factors in this population (symptoms, documented or suspected exposure, and other potential factors), increases the pre-test probability of a positive result and therefore the positive predictive value of the test.

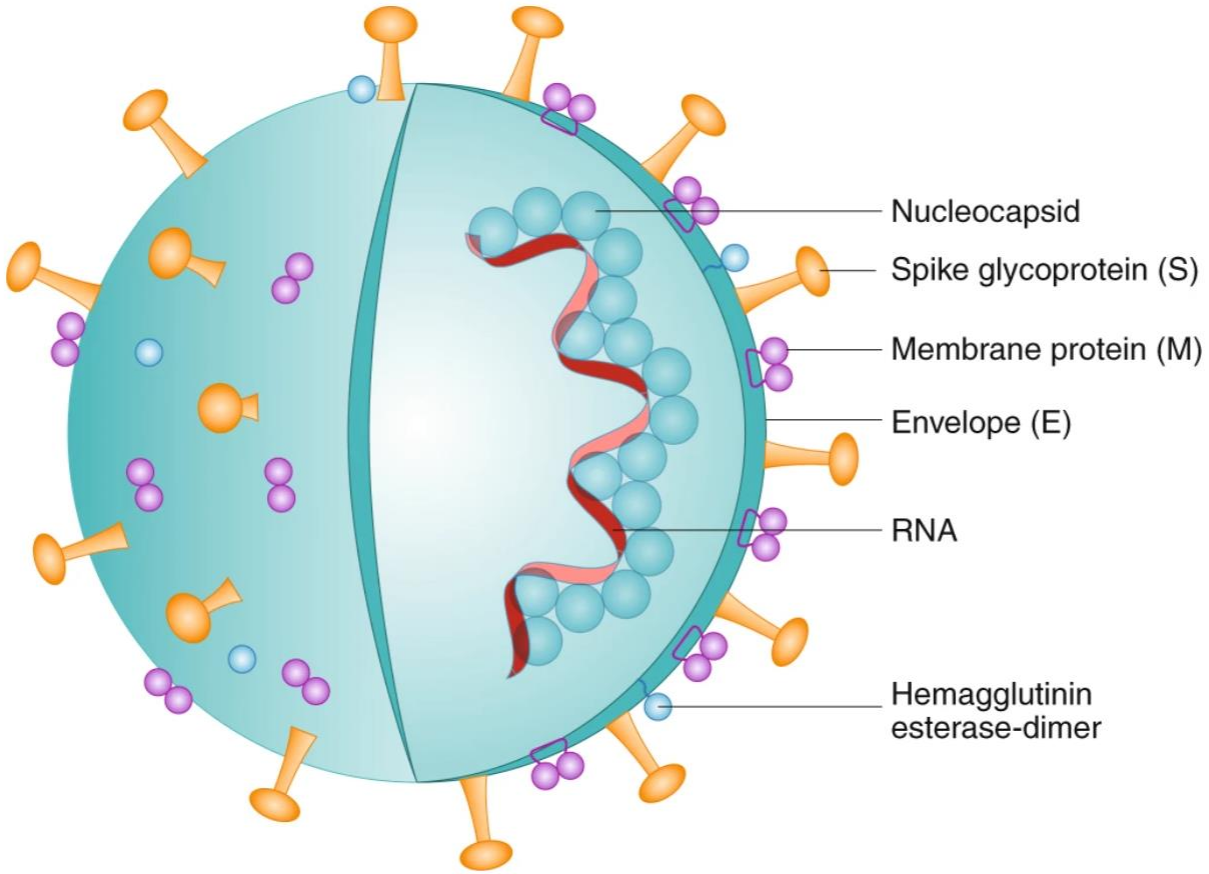
Screening testing: A variety of Guidance documents exist providing recommended screening strategies for a range of entities, including nursing homes, workplaces, schools and correctional facilities to maximize the utilization of testing at different sensitivities and specificities.

Surveillance testing: Surveillance testing is used to gain information at a population level, rather than an individual level, is performed on de-identified specimens, and results of surveillance testing are only returned in aggregate to the requesting institution.

Interim Guidance for Rapid Antigen Testing for SARS-CoV-2, CDC (Last updated September 4, 2020)
https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html

Antigen Testing: SARS-CoV-2 Virion Structure

From: Immune-mediated approaches against COVID-19



Schematic representation of SARS-CoV-2 structure. This is an enveloped, positive-sense RNA virus with four main structural proteins, including spike (S) and membrane (M) glycoproteins, as well as envelope (E) and nucleocapsid (N) proteins.

Florindo, HF et al mmune-mediated approaches against COVID-19 Nature Nanotechnology volume 15, pages630–645(2020) July 13, 2020 https://www.nature.com/articles/s41565-020-0732-3

Examples of Antigen Tests for Infectious Diseases

Rapid Influenza Tests: Rapid influenza diagnostic tests (RIDTs) are immunoassays that can identify the presence of influenza A and B viral nucleoprotein antigens in respiratory specimens, and display the result in a qualitative way (positive vs. negative)

- Sub-optimal test sensitivity (typically 50-70%), so false negative results are common, especially when influenza activity is high.
- Although specificity is high (typically 90-95%), false positive results can also occur, especially during times when influenza activity is low.

Respiratory Syncytial Virus: Most assays target the RSV fusion surface glycoprotein.

- RSV season peaks in winter.
- While most severe RSV occurs in infants, adults continue to be susceptible and are frequently infected

Rapid Influenza Diagnostic Tests, CDC https://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm

Rapid Antigen-based Testing for Respiratory Syncytial Virus https://www.medscape.com/viewarticle/782256_4

FDA EUAs Issued for COVID-19 Antigen Tests

Date EUA Issued or Last Updated	Entity	Diagnostic (Most Recent Letter of Authorization) and Date EUA Originally Issued	Attributes	Authorized Setting(s)[1]	Authorization Documents[2]
10/23/2020	Celltrion USA, Inc.	Sampinute COVID-19 Antigen MIA 10/23/2020	Magnetic Force-assisted Electrochemical Sandwich Immunoassay (MESIA)	H, M	HCP, Patients, IFU
10/13/2020	Access Bio, Inc.	CareStart COVID-19 Antigen test 10/08/2020	Lateral Flow, Visual Read	H, M, W	HCP, Patients, IFU
10/02/2020	Quidel Corporation	Sofia 2 Flu + SARS Antigen FIA 10/02/2020	Lateral Flow, Fluorescence, Instrument Read, Multi-Analyte	H, M, W	HCP, Patients, IFU
08/26/2020	Abbott Diagnostics Scarborough, Inc.	BinaxNOW COVID-19 Ag Card 08/26/2020	Lateral Flow, Visual Read	H, M, W	HCP, Patients, IFU
08/18/2020	LumiraDx UK Ltd.	LumiraDx SARS-CoV-2 Ag Test 08/18/2020	Microfluidic Immunofluorescence Assay, Instrument Read	H, M, W	HCP, Patients, IFU
07/23/2020	Becton, Dickinson and Company (BD)	BD Veritor System for Rapid Detection of SARS-CoV-2 07/02/2020	Chromatographic Digital Immunoassay, Instrument Read	H, M, W	HCP, Patients, IFU
07/17/2020	Quidel Corporation	Sofia SARS Antigen FIA 05/08/2020	Lateral Flow, Fluorescence, Instrument Read	H, M, W	HCP, Patients, IFU

On August 26 there were only two COVID-19 antigen tests authorized by EUA. As of October 28, there are seven authorized antigen tests.

https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#individual-antigen

The BinaxNOW™ COVID-19 Ag Card

FACT SHEET FOR HEALTHCARE PROVIDERS

Abbott Diagnostics Scarborough, Inc.
BinaxNOW™ COVID-19 Ag Card

August 26, 2020

Coronavirus Disease 2019 (COVID-19)

This Fact Sheet informs you of the significant known and potential risks and benefits of the emergency use of the BinaxNOW COVID-19 Ag Card.

The BinaxNOW COVID-19 Ag Card is authorized for use using nasal swab specimens collected from individuals who are suspected of COVID-19 by their healthcare provider within the first seven days of the onset of

This test is to be performed only using nasal swab specimens collected from individuals who are suspected of COVID-19 by their healthcare provider within the first seven days of the onset of symptoms.

"A limited cohort of patients who presented with symptom onset greater than seven days were enrolled in the clinical study (n = 28). Although the sample size was relatively small, the positive agreement in this cohort was 75% (9/12) and negative agreement was 92% (11/12). Therefore, negative results in patients with symptom onset greater than seven days should be treated as presumptive and confirmed with a molecular assay if needed for clinical management."

The BinaxNOW™ COVID-19 Ag Card

FACT SHEET FOR PATIENTS

Abbott Diagnostics Scarborough, Inc.
BinaxNOW™ COVID-19 Ag Card

August 26, 2020

Coronavirus Disease 2019 (COVID-19)

You are being given this Fact Sheet because your sample(s) was tested for the Coronavirus Disease 2019 (COVID-19) using the BinaxNOW COVID-19 Ag Card.

This Fact Sheet contains information to help you understand the risks and benefits of using this test for the diagnosis of COVID-19. After reading this Fact Sheet, if you have questions or would like to discuss the information provided, please talk to your healthcare provider.

For the most up to date information on COVID-19 please visit the CDC Coronavirus Disease 2019 (COVID-19) webpage:
https://www.cdc.gov/COVID19

Why was my sample tested?
You were tested because your healthcare provider believes you may have been exposed to the virus that causes COVID-19 based on your signs and symptoms (e.g., fever, cough, difficulty breathing), and/or other risk factors and you are within the first seven days of the onset of symptoms.

What are the known and potential risks and benefits of the test?

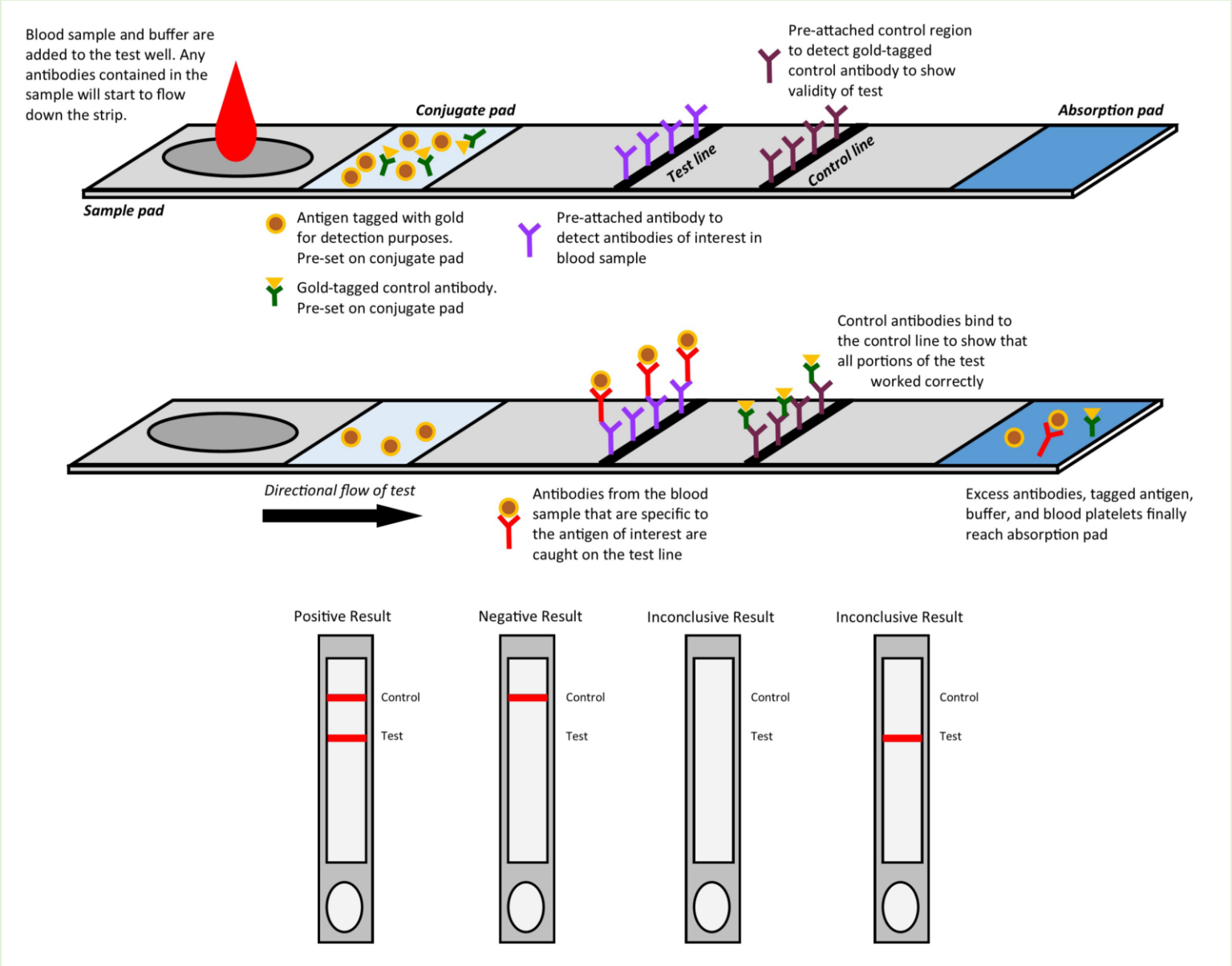
Potential risks include:

- Possible discomfort or other complications that can happen during sample collection.
- Possible incorrect test result (see below for more information).

Lateral Flow Technology

Johns Hopkins Bloomberg School of Public Health, Center for Health Security

https://www.centerforhealthsecurity.org/resources/COVID-19/serology/Serology-based-tests-for-COVID-19.html#sec2

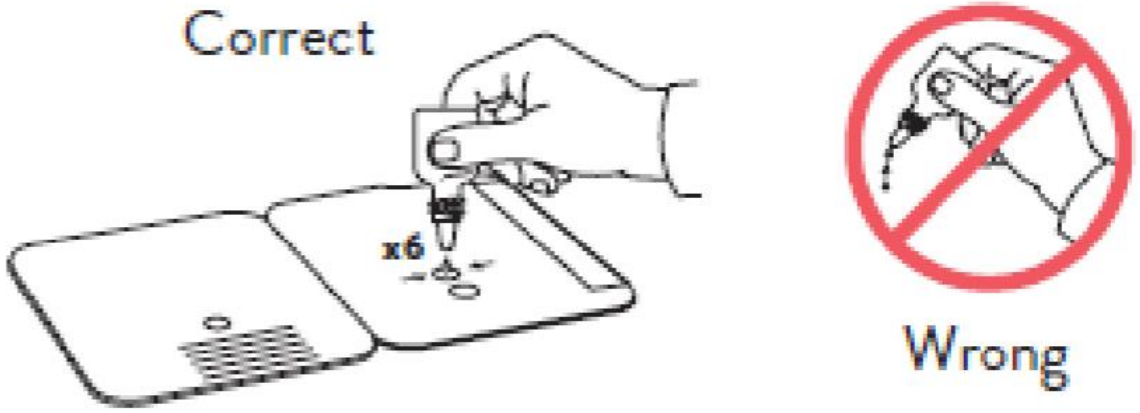


BinaxNOW™ COVID-19 Ag Card Test Procedures

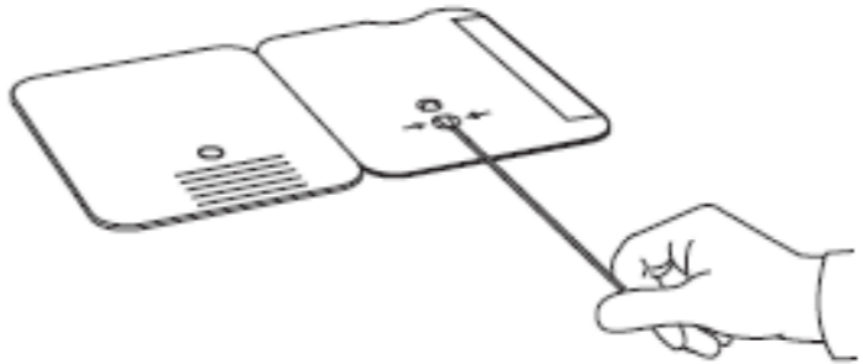
Procedure for Patient Specimens

Open the test card just prior to use, **lay it flat**, and perform assay as follows. **The test card must be flat when performing testing, do not perform testing with the test card in any other position.**

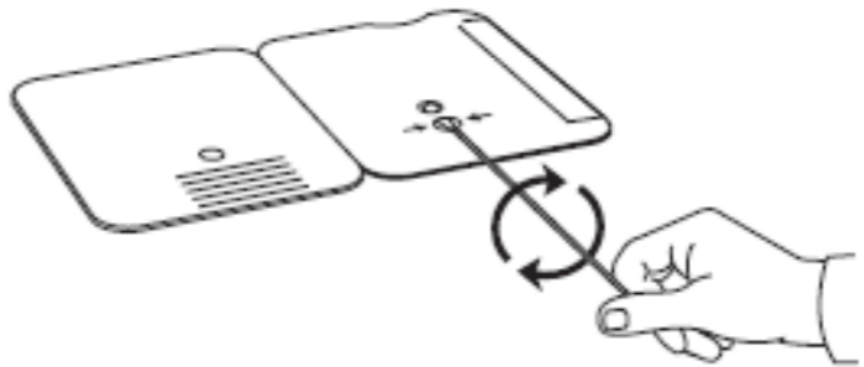
1. Hold Extraction Reagent bottle vertically. Hovering 1/2 inch above the **TOP HOLE,** slowly add **6 DROPS** to the **TOP HOLE** of the swab well. **DO NOT** touch the card with the dropper tip while dispensing.



2. Insert sample into **BOTTOM HOLE** and firmly push upwards so that the swab tip is visible in the **TOP HOLE**.

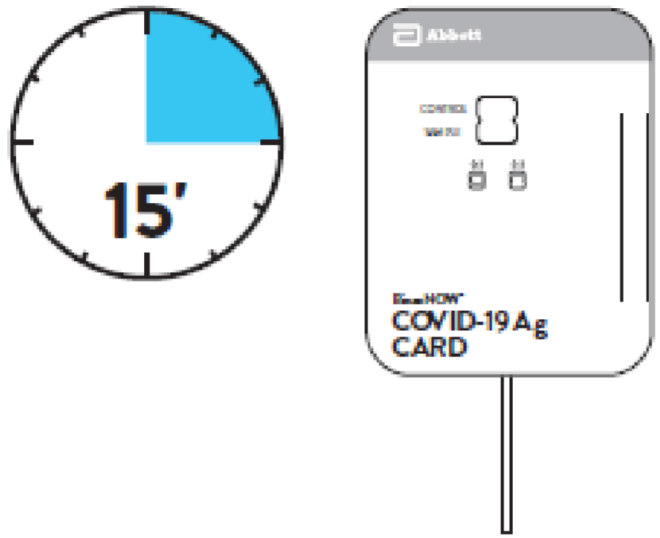


3. Rotate (twirl) swab shaft 3 times **CLOCKWISE** (to the right). Do not remove swab.



Note: False negative results can occur if the sample swab is not rotated (twirled) prior to closing the card.

4. Peel off adhesive liner from the right edge of the test card. Close and securely seal the card. Read result in the window 15 minutes after closing the card. In order to ensure proper test performance, it is important to read the result promptly at 15 minutes, and not before. Results should not be read after 30 minutes.



Note: When reading test results, tilt the card to reduce glare on the result window if necessary. Individuals with color-impaired vision may not be able to adequately interpret test results.

One difference when using the Control Swab:
Use 8 drops of the extraction reagent instead of 6 drops

Procedure for BinaxNOW™ Swab Controls

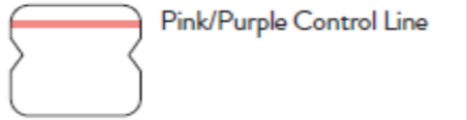
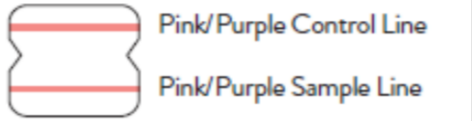
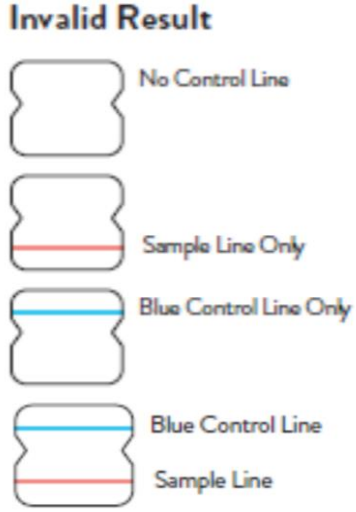
Open the test card just prior to use, lay it flat, and perform assay as follows.

1. Hold Extraction Reagent bottle vertically Hovering 1/2 inch above the **TOP HOLE,** slowly add **8 DROPS** to the **TOP HOLE** of the swab well. **DO NOT** touch the card with the dropper tip while dispensing.

BinaxNOW COVID-19 Antigen Card Test Interpretation

RESULT INTERPRETATION

Note: In an untested BinaxNOW COVID-19 Ag Card there will be a blue line present at the Control Line position. In a valid, tested device, the blue line washes away and a pink/purple line appears, confirming that the sample has flowed through the test strip and the reagents are working. If the blue line is not present at the Control Line position prior to running the test, do not use and discard the test card.

Negative A negative specimen will give a single pink/purple colored Control Line in the top half of the window, indicating a negative result. This Control Line means that the detection part of the test was done correctly, but no COVID-19 antigen was detected.	
Positive A positive specimen will give two pink/purple colored lines. This means that COVID-19 antigen was detected. Specimens with low levels of antigen may give a faint Sample Line. Any visible pink/purple colored line is positive.	
Invalid If no lines are seen, if just the Sample Line is seen, or the Blue Control Line remains blue, the assay is invalid. Invalid tests should be repeated.	

BinaxNOW™ Test Details and Limitations

- "This test detects both viable (live) and non-viable, SARS-CoV, and SARS-CoV-2." As such, this and similar antigen tests are not helpful in determining whether a new case or a previously confirmed case is currently infectious.
- Store kit at 2-30°C.
- Swabs in the kit are approved for use with BinaxNOWTM COVID-19 Ag Card. **Do not use other swabs."**
- Controls:
    - Internal Controls: "The pink-to-purple line at the "Control" position is an internal procedural control. If the test flows and the reagents work, this line will always appear."
    - External Controls: "BinaxNOWTM COVID-19 Ag Card kits contain a Positive Control Swab and Sterile Swabs that can be used as a Negative Control Swab."

BinaxNOW™ Test Details and Limitations

- "This test detects both viable (live) and non-viable, SARS-CoV, and SARS-CoV-2…
- …Authorized laboratories will collect information on the performance of your product and report to DMD/OHT7-OIR/OPEQ/CDRH (via email: CDRH-EUAReporting@fda.hhs.gov) and Abbott Diagnostics Scarborough, Inc. (via email: ts.scr@abbott.com, or via phone by contacting Abbott Diagnostics Scarborough, Inc. Technical Service at 1-800-257-9525) any suspected occurrence of false positive or false negative results and significant deviations from the established performance characteristics of your product of which they become aware
- All operators using your product must be appropriately trained…"

Additional notice is included in the kit insert warning that any deviation from the instructions will invalidate the reported specificity and sensitivity of the test

BinaxNOW™ Test Performance

- Clinical performance characteristics of BinaxNOW™ COVID-19 Ag Card was evaluated at seven (7) U.S. investigational sites in a prospective study in which patients were sequentially enrolled and tested. Testing was performed on 102 swabs by operators with no laboratory experience and who are representative of the intended users at CLIA waived testing sites.
- Two nasal swabs were collected from patients and tested using the BinaxNOW™ COVID-19 Ag Card at all study sites. An FDA Emergency Use Authorized real-time Polymerase Chain Reaction (RT-PCR) assay for the detection of SARS-CoV-2 was utilized as the comparator method for this study.

BinaxNOW™ Test Performance

BinaxNOW™ COVID-19 Ag Card Performance within 7 days of symptom onset against the Comparator Method

BinaxNOW™ COVID-19 Ag Card	Comparator Method		
	Positive	Negative	Total
Positive	34	1	35
Negative	1	66	67
Total	35	67	102
Positive Agreement: 34/35	97.1% (95% CI: 85.1% - 99.9%)		
Negative Agreement: 66/67	98.5% (95% CI: 92.0% - 100%)		

Proxy for Sensitivity

Proxy for Specificity

https://www.fda.gov/media/141570/download

A refresher regarding Sensitivity and Specificity

"In general, these POC antigen tests have a lower sensitivity, but similar specificity, for detecting SARS-CoV-2 compared to reverse-transcriptase polymerase chain reaction (RT-PCR) tests."

Mnemonics:

Sensitivity = TP/TP+FN ("SNOUT:" For highly sensitive tests, a negative tends to rule the condition out)

Specificity = TN/TN+FP ("SPIN:" For highly specific tests, a positive tends to rule the condition in)

...dependent upon pre-test probability (e.g. prevalence in your population)

Considerations for Use of SARS-CoV-2 Antigen Testing in Nursing Homes, CDC (Updated October 23, 2020)
https://www.cdc.gov/coronavirus/2019-ncov/hcp/nursing-homes-antigen-testing.html

Utilizing a test with lower sensitivity in low-prevalence populations: The FDA Addresses Off-Label Use

"For licensed health care practitioners who are prescribing or administering an authorized SARS-CoV-2 diagnostic test to be used off-label (outside the authorization) to screen *asymptomatic* [emphasis added] individuals not suspected of having COVID-19, we recommend they consider the information below, as well as the HHS guidance on PREP Act coverage.[1]

[1] FAQs on Testing for COVID-19: FDA Website, Q: Does the FDA have recommendations for health care providers using SARS-CoV-2 diagnostic tests for screening asymptomatic individuals for COVID-19? https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2#general

The Public Readiness and Emergency Preparedness Act (PREP Act)

Current Declarations

COVID-19 PREP Act Declarations

- Prep Act Guidance for Pharmacies
- Guidance for PREP Act Coverage for COVID-19
- Guidance for PREP Act Coverage for COVID-19 Screening Tests at Nursing Homes, Assisted-Living Facilities, Long-Term-Care Facilities, and other Congregate Facilities(August 31, 2020)
- Congregate Facilities(August 31, 2020)
- countermeasures pursuant to the CARES Act OGC Advisory Opinion on PREP Act Declaration
- Advisory Opinion 02-02 on the PREP Act and the Secretary's Declaration under the Act
- Second Amendment to Declaration under the PREP Act for Medical Countermeasures against COVID-19
- Third Amendment to Declaration under the PREP Act for Medical Countermeasures Against COVID–19

All Other Current PREP Act Declarations

- Ebola Disease Vaccines - Amendment (effective December 1, 2018)
- Ebola Disease Therapeutics - Amendment (effective December 1, 2018)
- Nerve Agents and Certain Insecticides (Organophosphorus and/or Carbamate) Countermeasures (effective April 11, 2017)
- Zika Virus Vaccines (effective August 1, 2016)
- Pandemic Influenza Medical Countermeasures (amended effective January 1, 2016)
- Anthrax Medical Countermeasures (amended effective January 1, 2016)
- Acute Radiation Syndrome Medical Countermeasures (amended effective January 1, 2016)
- Botulinum Toxin Medical Countermeasures (amended effective January 1, 2016)
- Smallpox Medical Countermeasures (amended effective January 1, 2016)

- Passed in 2005 to protect vaccine manufacturers from liability in the event of a declared public health emergency, at the time addressing potential liability for clinical trials of avian influenza vaccine.
- On March 10, 2020, the Secretary issued a Declaration under the PREP Act for medical countermeasures against COVID–19 (85 FR 15198, Mar. 17, 2020)

https://www.govinfo.gov/content/pkg/FR-2020-08-24/pdf/2020-18542.pdf

https://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx

https://www.federalregister.gov/documents/2020/03/17/2020-05484/declaration-under-the-public-readiness-and-emergency-preparedness-act-for-medical-countermeasures

Utilizing a test with lower sensitivity in low-prevalence populations: The FDA Addresses Off-Label Use

"According to FDA,
…when screening asymptomatic individuals, health care providers should consider using a highly sensitive test, especially if rapid turnaround times are available. If highly sensitive tests are not feasible, or if turnaround times are prolonged, health care providers may consider use of less sensitive point-of-care tests, even if they are not specifically authorized for this indication (commonly referred to as "off-label"). For congregate care settings, like nursing homes or similar settings, repeated use of rapid point-of-care testing may be superior for overall infection control compared to less frequent, highly sensitive tests with prolonged turnaround times."[1]

[1] FAQs on Testing for COVID-19: FDA Website, Q: Does the FDA have recommendations for health care providers using SARS-CoV-2 diagnostic tests for screening asymptomatic individuals for COVID-19? https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2#general

Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance

Daniel B. Larremore[†1,2], Bryan Wilder[3], Evan Lester[6,5], Soraya Shehata[4,5], James M. Burke[6], James A. Hay[7,8], Milind Tambe[3], Michael J. Mina[‡7,8,9,*], and Roy Parker[§4,6,10,2,*]

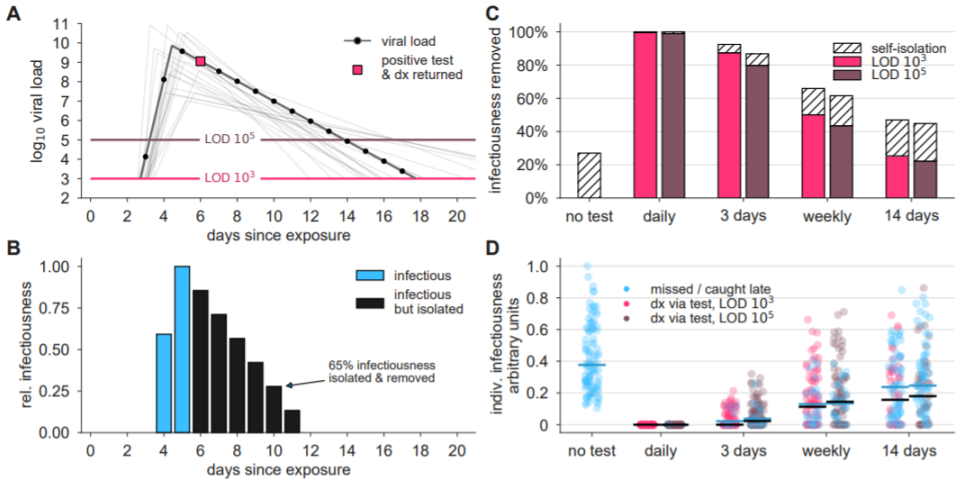


Figure 1: **Surveillance testing effectiveness depends on frequency.** (A) An example viral load trajectory is shown with LOD thresholds of two tests, and a hypothetical positive test on day 6, two days after peak viral load. 20 other stochastically generated viral loads are shown to highlight trajectory diversity (light grey; see Methods). (B) Relative infectiousness for the viral load shown in panel A pre-test, totaling 35% (blue) and post-isolation, totaling 65% (black). (C) Surveillance programs using tests at LODs of 10^3 and 10^5 at frequencies indicated were applied to 10,000 individuals' trajectories of whom 35% would undergo symptomatic isolation near their peak viral load if they had not been tested and isolated first. Total infectiousness removed during surveillance (colors) and self isolation (hatch) are shown for surveillance as indicated, relative to total infectiousness with no surveillance or self-isolation. (D) The impact of surveillance on the infectiousness of 100 individuals is shown for each surveillance program and no testing, as indicated, with each individual colored by test if their infection was detected during infectiousness (medians, black lines) or colored blue if their infection was missed by surveillance or detected positive *after* their infectious period (medians, blue lines). Units are arbitrary and scaled to the maximum infectiousness of sampled individuals.

- Turnaround times modelled were 48 hours, which may or may not be consistent with local experience.
- Isolation while awaiting test results would mitigate much of the effect, but could only be instituted in patients with reason for isolation (e.g. symptomatic, exposed etc…)

Larremore, D et al Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance medRxiv September 8, 2020 https://www.medrxiv.org/content/10.1101/2020.06.22.20136309v3.full.pdf

A Revised EUA Template for Antigen Test Developers from the FDA

October 26, 2020 Revision

Contains Nonbinding Recommendations

EXAMPLE TEMPLATE:

A. PURPOSE FOR SUBMISSION

Emergency Use Authorization (EUA) request for distribution and/or use of the ***[test name]*** to ***[indicate labs, if applicable]*** for the *in vitro* qualitative detection of antigen from the SARS-CoV-2 in ***[add all claimed specimen types, e.g., nasopharyngeal/ oropharyngeal swabs, sputa, BAL, and serum, etc.]*** from patients who are suspected of COVID-19 by a healthcare provider ***[within the first [insert number] days of symptom onset, or for screening of individuals without symptoms or other reasons to suspect COVID-19 infection, if applicable]***. Additional testing and confirmation procedures should be performed in consultation with public health and/or other authorities to whom reporting is required. Test results should be reported in accordance with local, state, and federal regulations.

If you plan to request authorization to test specimens collected with a home specimen collection kit, please refer to the Home Specimen Collection Molecular Diagnostic Template[4] ***and include any relevant information in this request.***

B. MEASURAND

F. PROPOSED INTENDED USE

1) **Intended Use: Example text is provided below for a qualitative antigen test, but could be adapted according to the specific emergency situation addressed by the device, proposed intended use population, testing sites, or performance characteristics. Please note that if you seek authorization for testing at point of care (POC) sites or for asymptomatic screening, you should provide data from your clinical validation studies to support such use.**

May 11, 2020 Revision

Contains Nonbinding Recommendations

EXAMPLE TEMPLATE:

A. PURPOSE FOR SUBMISSION

Emergency Use Authorization (EUA) request for distribution and/or use of the ***[test name]*** to ***[indicate labs, if applicable]*** for the *in vitro* qualitative detection of antigen from the SARS-CoV-2 in ***[add all claimed specimen types, e.g., nasopharyngeal/ oropharyngeal swabs, sputa, BAL, stool, and serum, etc.]*** from patients who are suspected of COVID-19 by a healthcare provider. Additional testing and confirmation procedures should be performed in consultation with public health and/or other authorities to whom reporting is required. Positive results should also be reported in accordance with local, state, and federal regulations. Performance is unknown in asymptomatic patients.

B. MEASURAND

Specific antigen(s) from the SARS-CoV-2 **[*please specify the targeted antigen(s)*]**.

C. APPLICANT

[Official name, address and contact information of applicant]

A. PROPOSED INTENDED USE

1) **Intended Use: Example text is provided below for a qualitative antigen test but may be adapted according to the specific emergency situation addressed by the device.**

FDA Response to inquiries regarding the use of lower sensitivity antigen tests at Point of Care (POC)

"As discussed in the EUA template, diagnostic POC tests are generally expected to demonstrate positive and negative agreement of ≥ 95%. However, positive agreement of ≥ 80% may be appropriate with appropriate limitations added to the intended use that would mitigate the risk of false negative results. For example, negative results may be considered presumptive negative if the demonstrated PPA is lower than 95%."

https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2#general-screeningasymptomatic

BinaxNOW™ Test Performance

BinaxNOW™ COVID-19 Ag Card Performance within 7 days of symptom onset against the Comparator Method

BinaxNOW™ COVID-19 Ag Card	Comparator Method		
	Positive	Negative	Total
Positive	34	1	35
Negative	1	66	67
Total	35	67	102
Positive Agreement: 34/35	97.1% (95% CI: 85.1% - 99.9%)		
Negative Agreement: 66/67	98.5% (95% CI: 92.0% - 100%)		

Proxy for Sensitivity

Proxy for Specificity

https://www.fda.gov/media/141570/download

Positive Predictive Value of BinaxNOW COVID-19 Antigen Card for Different Populations (Assumption: RT-PCR comparator test as reference test is infallible)

1) **The Validation Test Population** (See previous slide): 102 swabs collected within 7 days of symptom onset, with a population prevalence of disease of 34.3%

True positives: 34
False positives: 1
True negatives: 66
False negatives: 1

Positive Agreement (proxy for sensitivity): 97.1%
Negative Agreement (proxy for specificity): 98.5%
Positive Predictive Value: 97.1%
Negative Predictive Value: 98.5%

2) **Imaginary population with 5% disease prevalence:** 100 tests, the following values based upon the above calculated Sensitivity and Specificity of the test with a population prevalence of disease of 5% and specimen collection within 7 days of onset of disease/symptoms.

True positives: 4855
False Positives: 1425
True negatives: 93575
False negatives: 145

Positive Agreement (proxy for sensitivity): 97.1%
Negative Agreement (proxy for specificity): 98.5%
Positive Predictive Value: 77.3%
Negative Predictive Value: 99.8%

Table 3. Relationship between pre-test probability and the likelihood of positive and negative predictive values

Pretest Probability*	Negative Predictive Value**	Positive Predictive Value**	Impact on Test Results
Low	High	Low	Increased likelihood of False Positives Increased likelihood of True Negatives
High	Low	High	Increased likelihood of True Positives Increased likelihood of False Negatives

*Sensitivity and specificity of tests are generally stable and not affected by pretest probability.

**Predictive values are affected by pretest probability.

Definitions

Pretest probability: Probability of a patient having an infection before the test result is known; based on the proportion of people in a community with the disease at a given time (prevalence) and the clinical presentation of the patient.

Negative predictive value: Probability that a patient who has a negative test result truly does not have the infection.

Positive Predictive Value: Probability that a patient who has a positive test result truly does have the infection.

False Positive Result: A test result indicating the infection is present when it is not.

True Negative Result: A test result correctly indicating that the infection is not present.

False Negative Result: A test result indicating the infection is not present when it is.

True Positive Result: A test result correctly indicating that the infection is present.

Antigen Test Name	Date EUA Authorized [Antigen]	Specimen	Positive Percent Agreement	Negative Percent Agreement	Positive Predictive Value at Population Prevalence of 5%	Negative Predictive Value at Population Prevalence of 5%	Testing Window: Days from Symptom Onset	Limits of Detection ($TCID_{50}$) [time for test]
BinaxNOW COVID-19 Antigen Card	8/26/2020 [nucleocapsid]	Mid Turbinate Nasal Swab	97.1% (N=102)	98.5% (N=102)	77.3% (N=102)	99.8% (N=102)	7 days	22.5/swab [15-30 min]
Quidel Sofia SARS Antigen FIA	5/8/2020 [nucleocapsid]	Nasal or Nasopharyngeal	96.7% (N=209)	100% (N=209)	100% (N=209)	99.8% (N=209)	5 days	113/ml [15-30 min]
Quidel Sofia2 Influenza A/B + SARS FIA	10/2/2020 [nucleocapsid]	Nasal or Nasopharyngeal	95.2% (N=164)	100% (N=164)	100% (N=164)	99.7% (N=164)	5 days	91.7/ml [15-30 min]
CareStart COVID-19 Antigen Test	10/8/2020 [nucleocapsid]	Nasopharyngeal	88.37% (N=106)	100% (N=106)	100% (N=106)	99.4% (N=106)	5 days	800/ml direct swab [10-15 min]
BD Veritor System for COVID-19	7/2/2020 [nucleocapsid]	Nasal Swab	84% (N=195)	100% (N=195)	100% (N=195)	99.16% (N=195)	5 days	140/ml [15-30 min]
LumiraDx SARS-CoV-2 Ag Test	8/18/2020 [nucleocapsid]	Nasal Swab	97.6% (N=257)	96.6% (N=257)	60.2% (N=257)	99.87% (N=257)	12 days	32/ml [approx. 15 minutes]
Sampinute COVID-19 Antigen MIA	10/23/2020 [spike]	Nasopharyngeal	94.4% (N=72)	100% (N=72)	100% (N=72)	99.7% (N=72)	5 days	30/ml [10-15 min]

Note: CLIA Waiver Certificate is not sufficient qualification for the Sampinute test

Hypothetical Positive and Negative Predictive Values for the BD Veritor Antigen Test System at Different Prevalence Levels

Table 2

Hypothetical Positive and Negative Predictive Values for the BD Veritor System for Rapid Detection of SARS-CoV-2 compared to PCR

			PPV		NPV	
Prevalence	Sensitivity	Specificity	Estimate	95% C.I.	Estimate	95% CI
1.0%	84.0% (26/31)	100.0% (195/195)	100.0%	(33.2%,100.0%)	99.8%	(99.7%, 99.9%)
2.0%			100.0%	(50.1%,100.0%)	99.7%	(99.3%, 99.9%)
5.0%			100.0%	(72.1%,100.0%)	99.2%	(98.3%, 99.7%)
10.0%			100.0%	(84.5%,100.0%)	98.2%	(96.4%, 99.4%)
13.7%			100.0%	(88.6%,100.0%)	97.5%	(94.9%, 99.1%)
15.0%			100.0%	(89.7%,100.0%)	97.2%	(94.4%, 99.0%)
20.0%			100.0%	(92.5%,100.0%)	96.1%	(92.2%, 98.7%)
25.0%			100.0%	(94.2%,100.0%)	94.9%	(89.9%, 98.2%)

EXPLANATION OF TERMS:

C.I.: Confidence Interval

PPV: Positive Predictive Value = True Positives / True Positive + False Positive

NPV: Negative Predictive Value = True Negatives / True Negative + False Negative

Sample scenarios influencing risk and pre-test probability

Sample factors, from higher to lower added risk, that increase the probability of infection, and therefore the positive predictive value of the test, include:

- The presence of symptoms in the person being tested
- The likely prevalence of COVID-19 in the tested population, such as during an outbreak in a nursing home or in a high prevalence community
- Recent exposure to a confirmed case of COVID-19
- Recent exposure to a suspected case of COVID-19
- Recent travel to an area or region with active COVID-19 outbreaks without adherence to masking and distancing recommendations
- Recent travel to an area or region with active COVID-19 outbreaks without adherence to masking and distancing recommendations

A Summary Statement from the CDC

"CDC recommends that laboratory and testing professionals who perform rapid antigen testing should determine infection prevalence based on a rolling average of the positivity rate of their own SARS-CoV-2 testing over the previous 7–10 days. Infection prevalence at the time of testing, as well as the clinical context of the recipient of the test, impacts pretest probability. If a specific testing site, such as a nursing home, has a positivity rate near zero, the prevalence of disease in the community (e.g., cases per population) should instead be used to help determine pretest probability. Rapid antigen tests should be interpreted in the context of the prevalence of infection or disease, the device's performance characteristics and instructions for use, and the patient's clinical signs, symptoms, and history."

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

For *Diagnostic* and *Screening* Testing:

"CMS will temporarily exercise enforcement discretion for the duration of the COVID-19 public health emergency under CLIA for the use of SARS-CoV-2 POC antigen tests on asymptomatic individuals. Specifically, CMS will not cite facilities with a CLIA Certificate of Waiver when SARS-CoV-2 POC antigen tests are performed on asymptomatic individuals, as described in the FDA FAQ."

For *Surveillance* Testing:

Laboratory and testing professionals who conduct surveillance testing for SARS-CoV-2 with rapid antigen tests are not obligated to comply with these FDA and CLIA requirements. However, CDC recommends that facilities that conduct surveillance testing for SARS-CoV-2 with antigen tests should use an antigen test that has been authorized for use

https://www.cms.gov/files/document/clia-poc-ag-test-enforcement-discretion.pdf

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

Additional BinaxNOW™ COVID-19 Ag Card Details

The performance of BinaxNOW™ COVID-19 Ag Card with positive results stratified by the comparator method cycle threshold (Ct) counts were collected and assessed to better understand the correlation of assay performance to the cycle threshold, estimating the viral titer present in the clinical sample. As presented in the table below, the positive agreement of the BinaxNOW™ COVID-19 Ag Card is higher with samples of a Ct count <33.

BinaxNOW™ COVID-19 Ag Card Performance against the Comparator Method – by Cycle Threshold Counts

BinaxNOW™ COVID-19 Ag Card	Comparator Method (POS by Ct Category)	
	POS (Ct < 33)	POS (Ct ≥ 33)
Positive	29	5
Negative	0	1
Total	29	6
Positive Agreement (95% CI)	100.0 (88.1, 100.0)	83.3 (35.9, 99.6)

Potential Cross-Reactant		Test Concentration
Virus	Adenovirus	1.0 x 10^5 $TCID_{50}$/mL
	Human metapneumovirus (hMPV)	1.0 x 10^5 $TCID_{50}$/mL
	Rhinovirus	1.0 x 10^5 PFU/mL
	Enterovirus/Coxsackievirus B4	1.0 x 10^5 $TCID_{50}$/mL
	Human coronavirus OC43	1.0 x 10^5 $TCID_{50}$/mL
	Human coronavirus 229E	1.0 x 10^5 $TCID_{50}$/mL
	Human coronavirus NL63	1.0 x 10^5 $TCID_{50}$/mL
	Human parainfluenza virus 1	1.0 x 10^5 $TCID_{50}$/mL
	Human parainfluenza virus 2	1.0 x 10^5 $TCID_{50}$/mL
	Human parainfluenza virus 3	1.0 x 10^5 $TCID_{50}$/mL
	Human parainfluenza virus 4	1.0 x 10^5 $TCID_{50}$/mL
	Influenza A	1.0 x 10^5 $TCID_{50}$/mL
	Influenza B	1.0 x 10^5 $TCID_{50}$/mL
	Respiratory Syncytial Virus A	1.0 x 10^5 PFU/mL
Bacteria	***Bordetella pertussis***	1.0 x 10^6 cells/mL
	Chlamydia pneumoniae	1.0 x 10^6 IFU/mL
	Haemophilus influenzae	1.0 x 10^6 cells/mL
	Legionella pnuemophila	1.0 x 10^6 cells/mL
	Mycoplasma pneumoniae	1.0 x 10^6 U/mL
	Streptococcus pneumoniae	1.0 x 10^6 cells/mL
	Streptococcus pyogenes (group A)	1.0 x 10^6 cells/mL
	Mycobacterium tuberculosis	1.0 x 10^6 cells/mL
	Staphylococcus aureus	1.0 x 10^6 org/mL
	Staphylococcus epidermidis	1.0 x 10^6 org/mL
	Pooled human nasal wash	N/A
Yeast	***Candida albicans***	1.0 x 10^6 cells/mL

- No cross-reactivity or interference was seen with the microorganisms in this chart when tested at the concentration presented.
- The comparison between SARS-CoV-2 nucleocapsid protein, MERS-CoV and human coronavirus HKU1 revealed that cross-reactivity cannot be ruled out. Homology for HKU1 and MERS-CoV is relatively low, at 37.8% across 95% of the sequence and 57.14% across 87% of the sequence, respectively.
- No high dose hook effect was observed when tested with up to a concentration of 1.6 x 105 TCID50/mL of heat inactivated SARS-CoV-2 virus with the BinaxNOW™ COVID-19 Ag Card.

Endogenous Interfering Substances

Substance	Active Ingredient	Concentration
Endogenous	Mucin	2% w/v
	Whole Blood	1% v/v
OTC Nasal Drops	Phenylephrine	15% v/v
OTC Nasal Gel	Sodium Chloride (i.e. NeilMed)	5% v/v
OTC Nasal Spray 1	Cromolyn	15% v/v
OTC Nasal Spray 2	Oxymetazoline	15% v/v
OTC Nasal Spray 3	Fluconazole	5% w/v
Throat Lozenge	Benzocaine, Menthol	0.15% w/v
OTC Homeopathic Nasal Spray 1	Galphimia glauca, Sabadilla,	20% v/v
OTC Homeopathic Nasal Spray 2	Zincum gluconium (i.e., Zicam)	5% w/v
OTC Homeopathic Nasal Spray 3	Alkalol	10% v/v
OTC Homeopathic Nasal Spray 4	Fluticasone Propionate	5% v/v
Sore Throat Phenol Spray	Phenol	15% v/v
Anti-viral Drug	Tamiflu (Oseltamivir Phosphate)	0.5% w/v
Antibiotic, Nasal Ointment	Mupirocin[1]	0.25% w/v
Antibacterial, Systemic	Tobramycin	0.0004% w/v

[1] Testing demonstrated false negative results at concentrations of 5 mg/mL (0.5% w/v). Standard dose of nasal ointment: 20 mg (2% w/w) of mupirocin in single-use 1-gram tubes.

Summary Tables

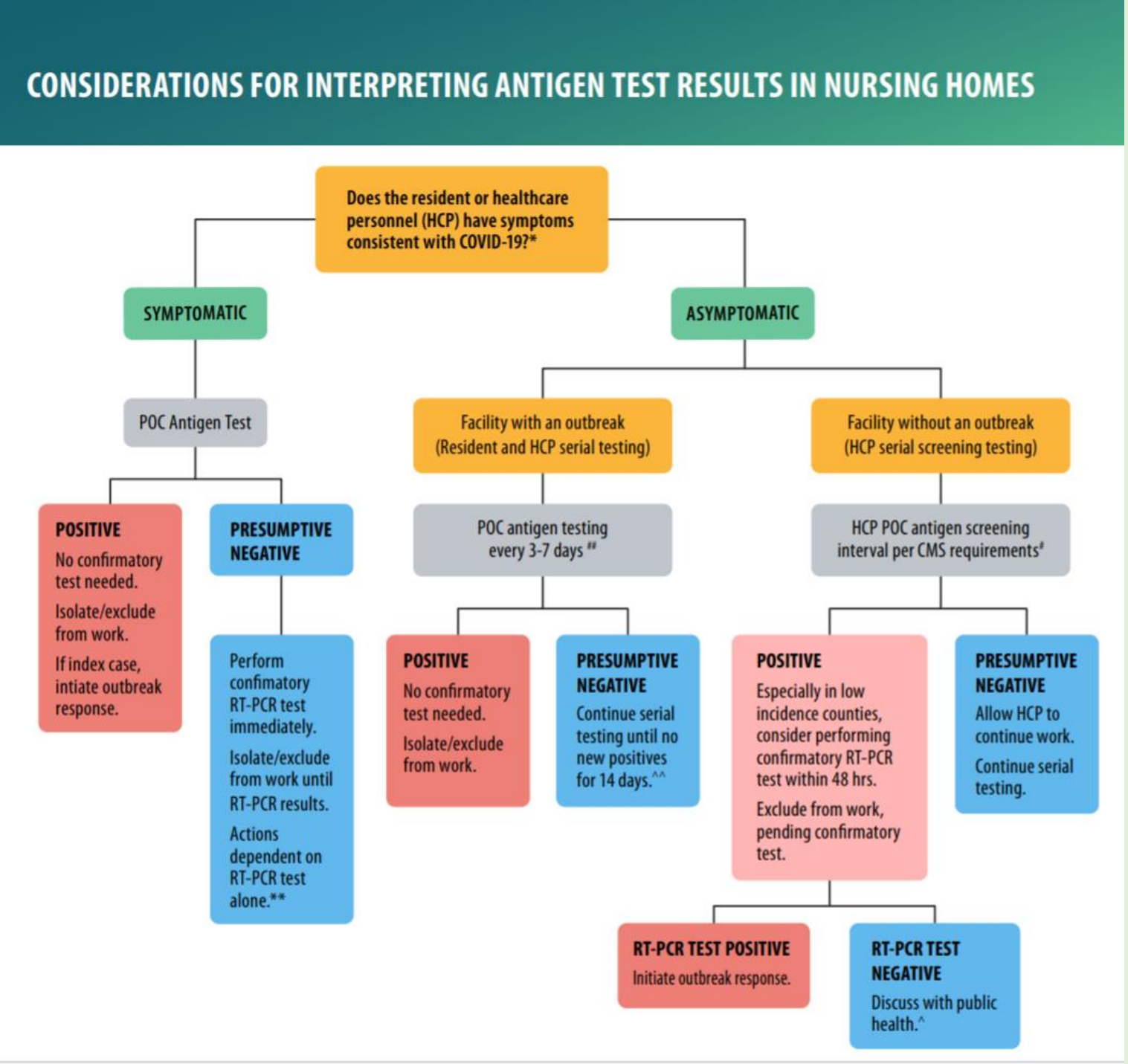
Table 1. Testing Strategies for SARS-CoV-2

	Diagnostic	Screening	Surveillance
Symptomatic or Known or Suspected Exposure	Yes	No	N/A
Asymptomatic without Known or Suspected Exposure	No	Yes	N/A
Characterize Incidence and Prevalence in the Community	N/A	N/A	Yes
Results may be Returned to Individuals	Yes	Yes	No
Results Returned in Aggregate to Requesting Institution	No	No	Yes

	Diagnostic	Screening	Surveillance
Results Reported to State Public Health Department	Yes	Yes	Only if requested; must be in aggregate
Testing can be performed in a CLIA-Certified Laboratory	Yes	Yes	Yes
Testing can be performed in a Non-CLIA-Certified Laboratory	No	No	Yes
Test System Must be FDA Authorized or Offered under the Policies in FDA's Guidance	Yes	Yes	No

Table 2. Summary of Some Differences between RT-PCR Tests and Antigen Tests

	RT-PCR Tests	Antigen Tests
Intended Use	Detect current infection	Detect current infection
Analyte Detected	Viral RNA	Viral Antigens
Specimen Type(s)	Nasal Swab, Sputum, Saliva	Nasal Swab
Sensitivity	High	Moderate
Specificity	High	High
Test Complexity	Varies	Relatively easy to use
Authorized for Use at the Point-of-Care	Most devices are not, some devices are	Yes
Turnaround Time	Ranges from 15 minutes to >2 days	Approximately 15 minutes
Cost/Test	Moderate	Low



Testing of symptomatic residents or HCP

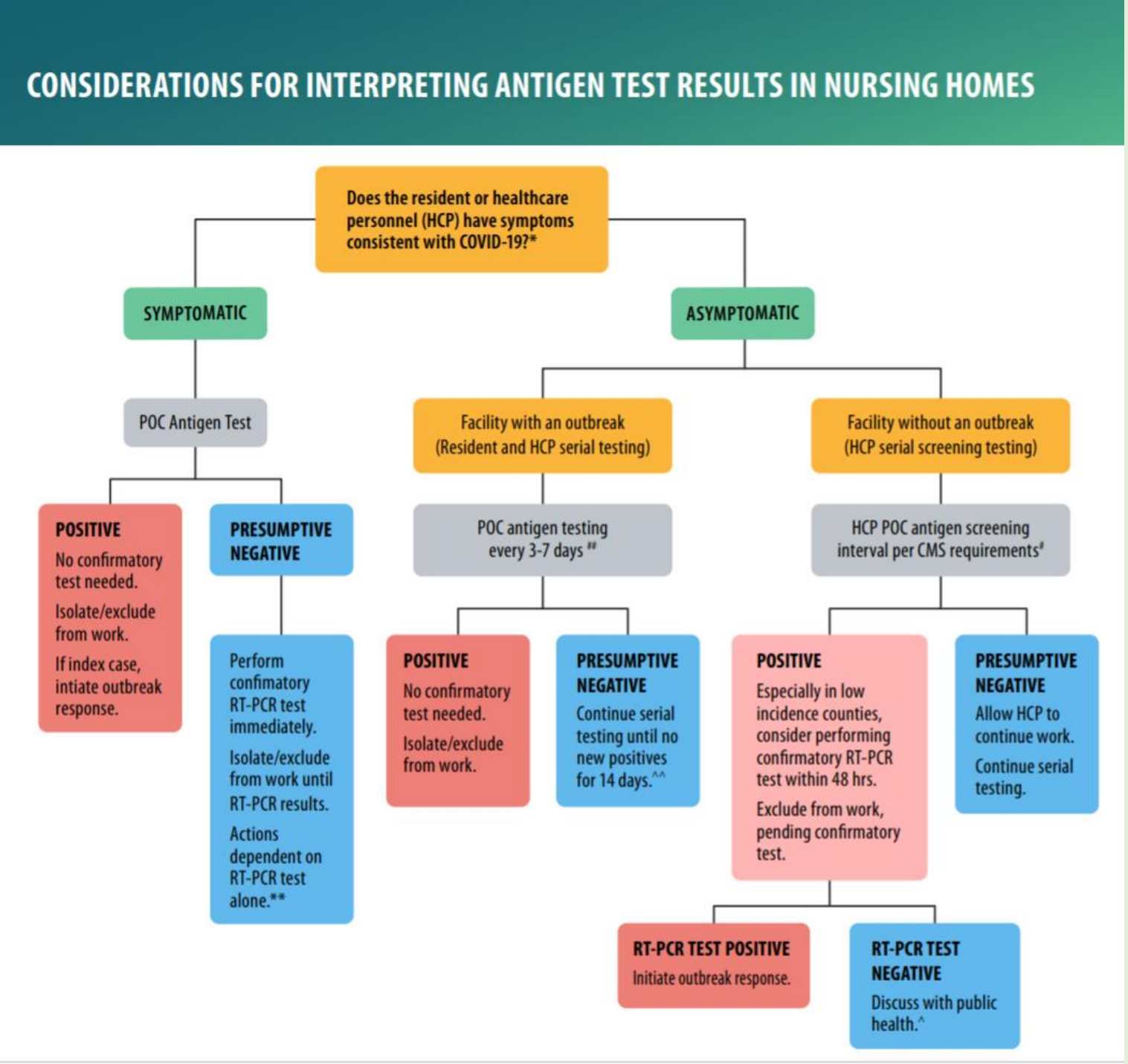
If an antigen test is positive, no confirmatory test is necessary.

- Residents should be placed in Transmission-Based Precautions or HCP should be excluded from work.
- If the resident or HCP is the first positive test for SARS-CoV-2 within the facility (i.e., an index case), an outbreak response should be initiated immediately.*

If an antigen test is presumptive negative, perform RT-PCR immediately (e.g., within 48 hours).

- Symptomatic residents and HCP should be kept in transmission-based precautions or excluded from work until RT-PCR results return.

https://www.cdc.gov/coronavirus/2019-ncov/hcp/nursing-homes-antigen-testing.html



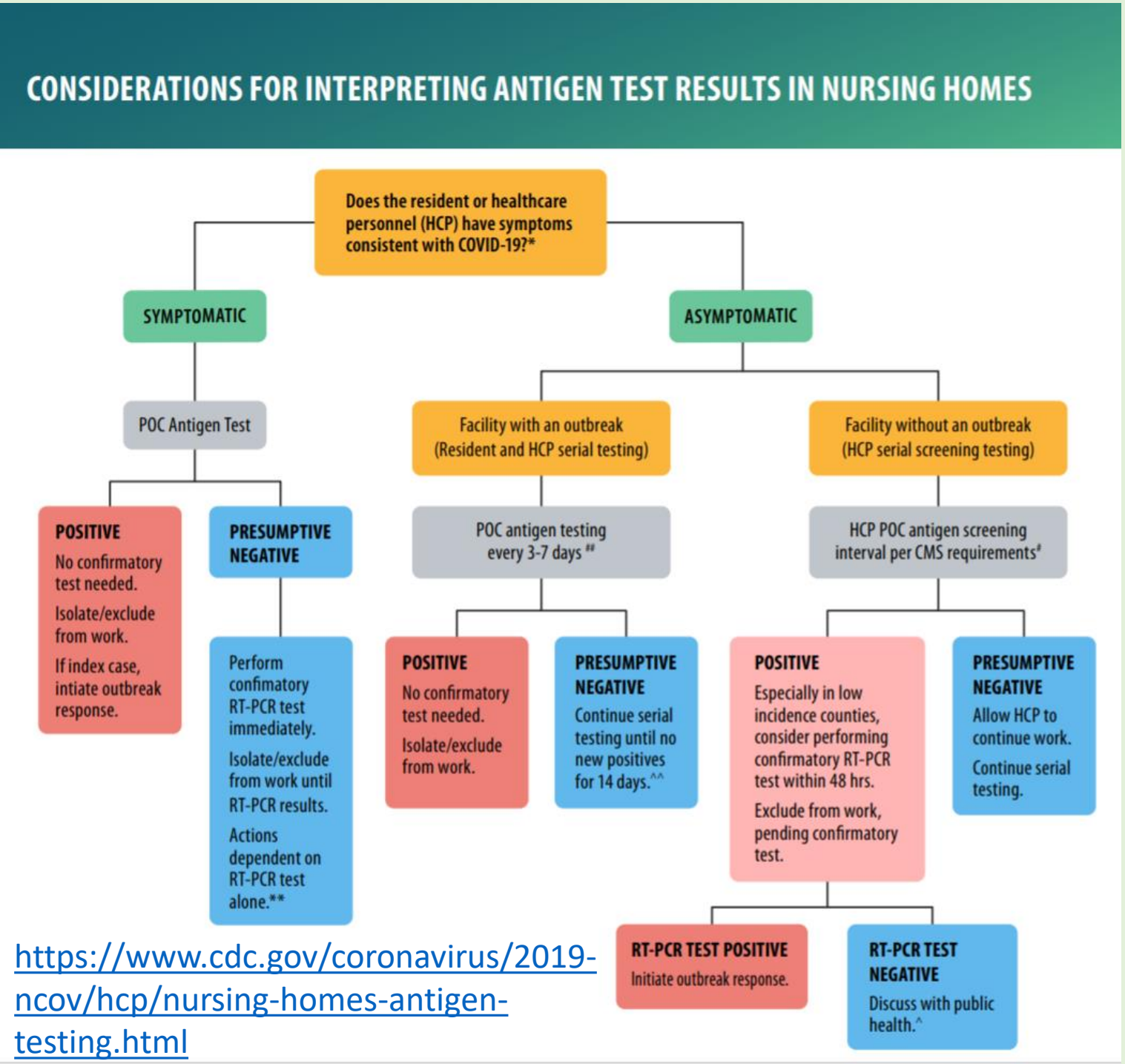
Testing of asymptomatic residents or HCP in nursing homes as part of an outbreak response*

If an antigen test is positive, no confirmatory test is necessary.

- Residents should be placed in transmission-based precautions, and HCP should be excluded from work.

If an antigen test is presumptive negative, residents should be placed in [appropriate precautions for facilities with an outbreak](). ative, residents should be placed in appropriate precautions for facilities with an outbreak.

https://www.cdc.gov/coronavirus/2019-ncov/hcp/nursing-homes-antigen-testing.html



https://www.cdc.gov/coronavirus/2019-ncov/hcp/nursing-homes-antigen-testing.html

Testing of asymptomatic HCP in nursing homes without an outbreak per CMS recommendations

CMS recommends initial testing of all HCP as part of the nursing home reopening process and serial testing of HCP at an interval based on local incidence of COVID-19.

If an antigen test is positive, perform confirmatory RT-PCR test within 48 hours of the antigen test, especially in counties with low prevalence. If confirmatory test is performed, HCP should be excluded from work until confirmatory test results are completed.

- If the confirmatory test is positive, then exclude the HCP from work and initiate an outbreak response including facility-wide testing of all residents and HCP.
- If the confirmatory test is negative, discuss results with the local public health department to determine how to interpret the discordant results and next steps.

Targeting Testing: To the Most Vulnerable…

"Certain settings and vulnerable populations in a community are at particularly high risk for transmission. This includes but is not limited to congregate settings such as nursing homes and other long-term care facilities, correctional facilities, and the homeless population."

Week ending October 11: ……60,491 deaths in nursing facilities
October 26, 2020: ……1,735 COVID-19 deaths in prisoners and
54 deaths in custody staff

https://data.cms.gov/stories/s/COVID-19-Nursing-Home-Data/bkwz-xpvg/
https://docs.google.com/spreadsheets/d/1X6uJkXXSO6eePLxw2e4JeRtM41uPZ2eRcOA_HkPVTk/edit#gid=1197647409
https://www.cdc.gov/coronavirus/2019-ncov/community/community-mitigation.html

Targeting Testing: To the Most Critical To the COVID-19 Response…

"In the United States as of Sept. 16, 2020:

- » At least 213 registered nurses have died of Covid-19 and related complications.
- » 124 (58.2 percent) of the 213 RNs who have died of Covid-19 and related complications are nurses of color…
- » At least 1,718 health care workers, including registered nurses, have died of Covid-19 and related complications."

https://act.nationalnursesunited.org/page/-/files/graphics/0920_Covid19_SinsOfOmission_Data_Report.pdf

https://www.cdc.gov/coronavirus/2019-ncov/community/community-mitigation.html

Targeting Testing: To Public Safety Workers…

https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/COVID-19/Updated-COVID-19-Testing-Guidance.aspx

https://www.cdc.gov/coronavirus/2019-ncov/community/community-mitigation.html

Questions and discussion regarding Antigen Testing…