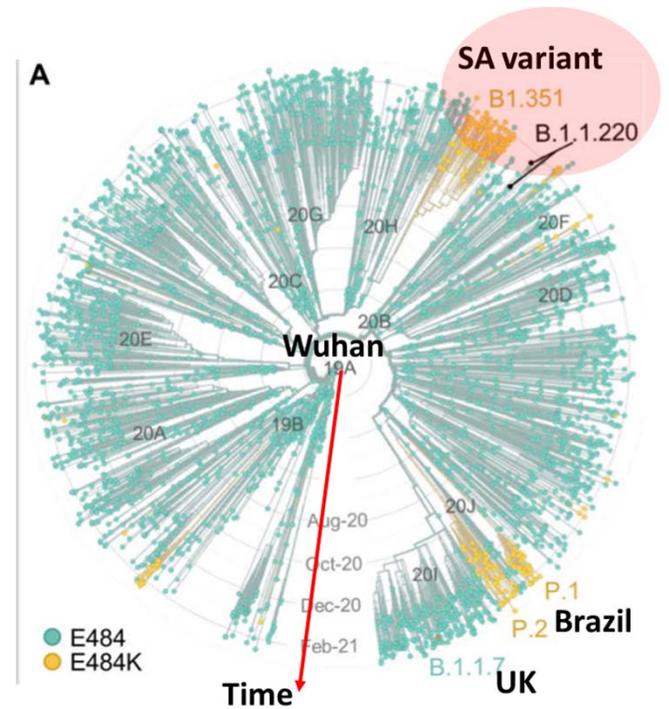


The Role of Antigen Tests in Controlling the COVID-19 Pandemic

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Supplemental Teaching Module; April 2021

If the PDF links fail, copy and paste the link into your browser



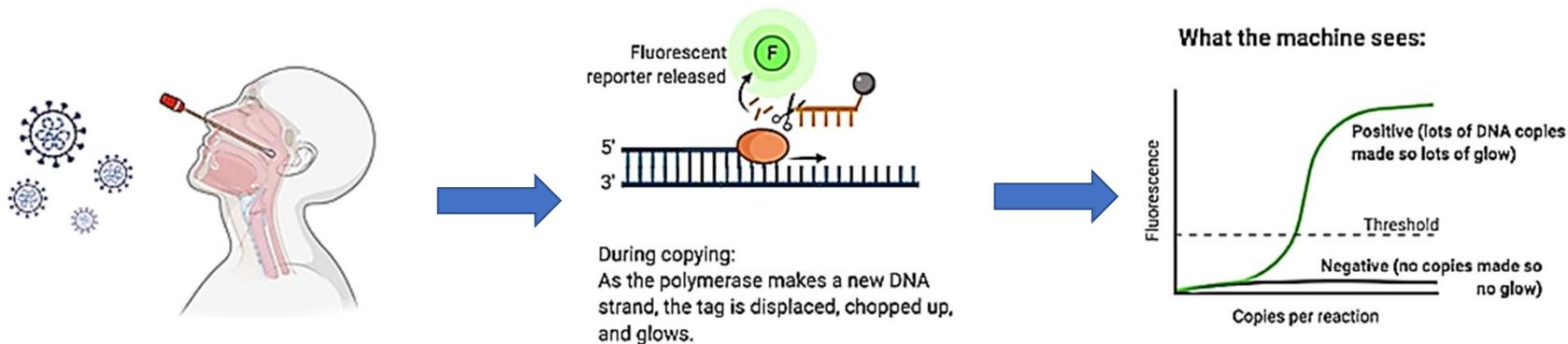
Control of SARS-CoV-2 Spread is More than Simply Finding It in a Nasal Swab

The role of testing in the control of the SARS-CoV-2 Pandemic cannot be underestimated.

The spread of this virus is dependent upon asymptomatic spread. It is designed to do this by damping the first immune step, the innate response (Interferon), allowing the infected subject to spread the virus unknowingly while the virus is making trillions of copies and invading tissues.

The **Polymerase Chain Reaction (PCR)** test is a precise and highly sensitive test to find even minute numbers of virus. It can identify an “infected” individual, presence of the virus on a contaminated surface, a strain of the virus like a specific variant, etc.

PCR is like a “copy machine” – it pairs a string of known DNA (or RNA; a primer) with one it finds in a sample and makes a copy. The process repeats to make 4 copies, 8 copies, 16 copies, 32 copies On up to billions of copies. The raw materials it uses (nucleotides) to duplicate are tagged with a fluorescent chemical and when used to make a copy released the fluorescent tag. The detector senses a threshold of fluorescence (source: <https://www.otago.ac.nz/biochemistry/research/otago736925.html>)



Control of SARS-CoV-2 Spread is More than Simply Finding It in a Nasal Swab

But finding the virus is only part of the “Control Equation” - We need to know how much virus.

This is termed the “**Ct score.**” The number of repeated duplicates to “see” fluorescence tells us how much virus we sampled from a person, a thing, or other source.

How much virus is in the sample is critical to know AND NOT JUST THAT IT IS “THERE”. This defines the infectivity of the sample or, the risk of passing sufficient virus to infect another person.

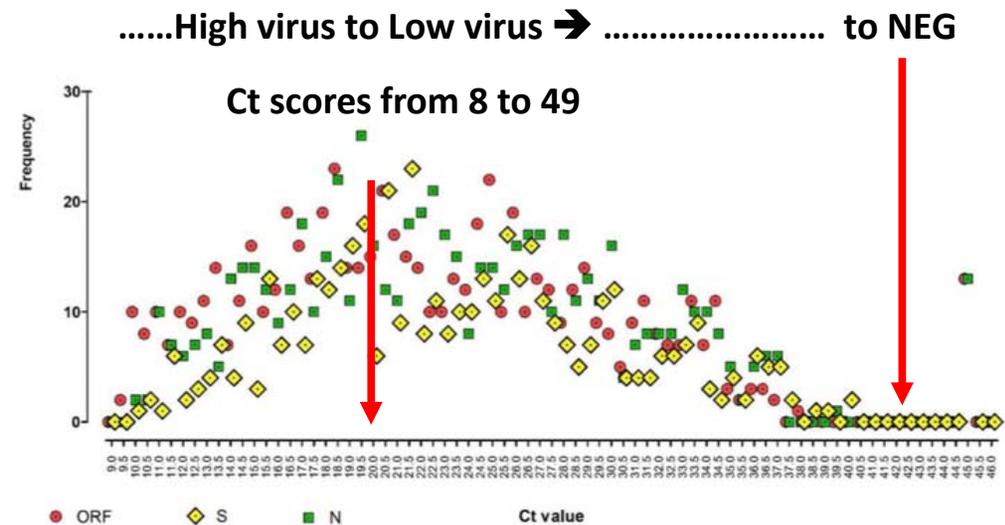
The greater the number of virus in a sample → the fewer the number of repeated cycles (Low Ct score)

A NEGATIVE PCR test is 40 cycles or greater with no fluorescence detected

The figure to the right is Ct scores and the relative frequency found for three sequences of the COVID virus: the ORF (open reading frame sequence), the N (nucleocapsid sequence) and the S (Spike sequence) used as the initial primers for pairing.

Infected subjects are noted as “fluorescent” with Ct scores from 8 (very high virus) to 39 (very low virus) and peaking around a Ct score of 20 (arrow).

Unfortunately: PCR Tests are reported as “POS” or “NEG” and we lose valuable information on the state of infection



What the Ct Score Tells Us is Who Gets Infected and Why?

It Really is “How Much You Breathe In”

Depends on the Time and Proximity to an Infected Person

Ct Scores of a Mixed Population

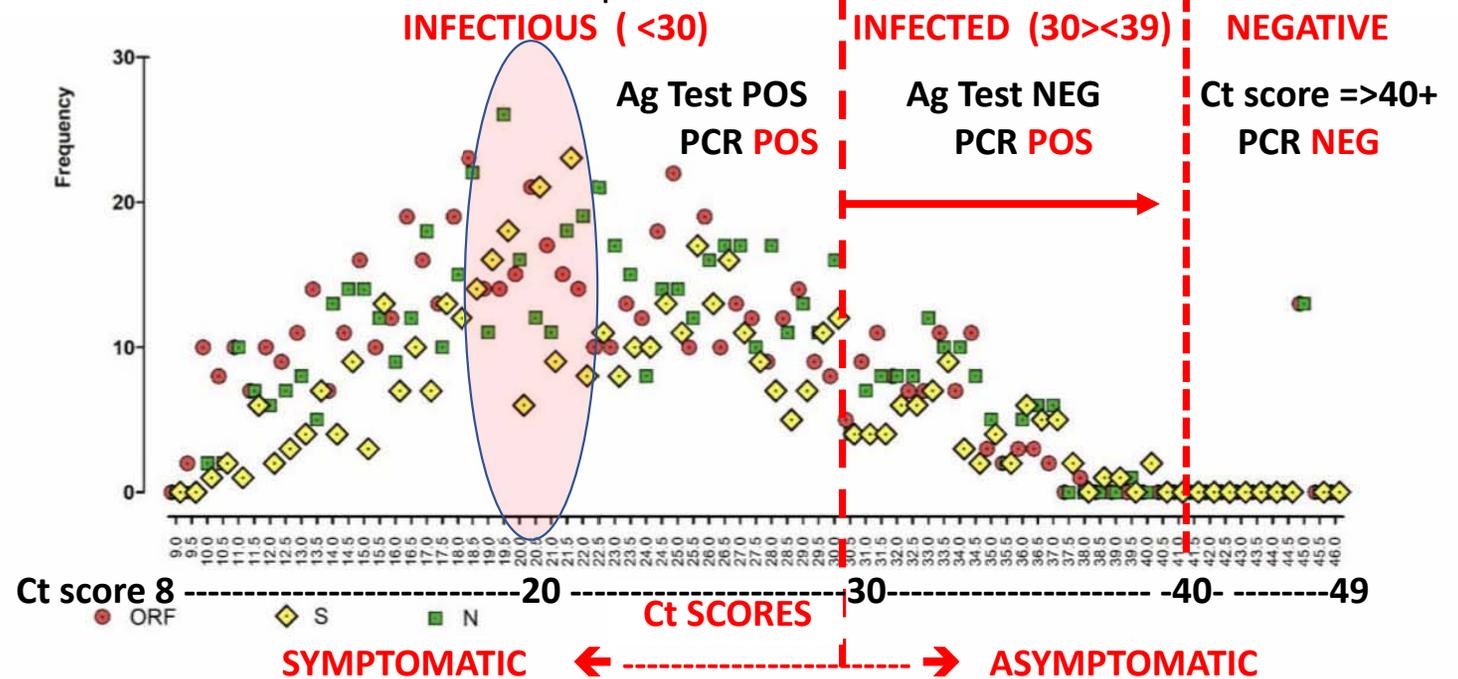


Figure 2: Dot-plot frequency analysis showing the relationship between three viral gene targets detected by the TaqPath RT-QPCR test, across the full range of Ct values. Y-axis is divided into a low frequency range of 0-30 and a high frequency range of 50-250. A Ct of 45 is artificially assigned to represent results where no signal was detected in that assay.

The graph shows the PCR Ct score for three viral components: The Open Reading Frame (ORF; RNA that makes proteins that help make more virus). The S (spike RNA) and the N segment (nucleocapsid RNA).

The point is to show you the Ct scores around 20 are heavy viral shedding and INFECTIOUS when Ct score is <30

(Most SURFACES max at Ct ~34)

Inference from PCR Ct Scoring

PCR Ct scoring is a fluorescent signal that is evident after several repeated cycles that double the gene identity each cycle.

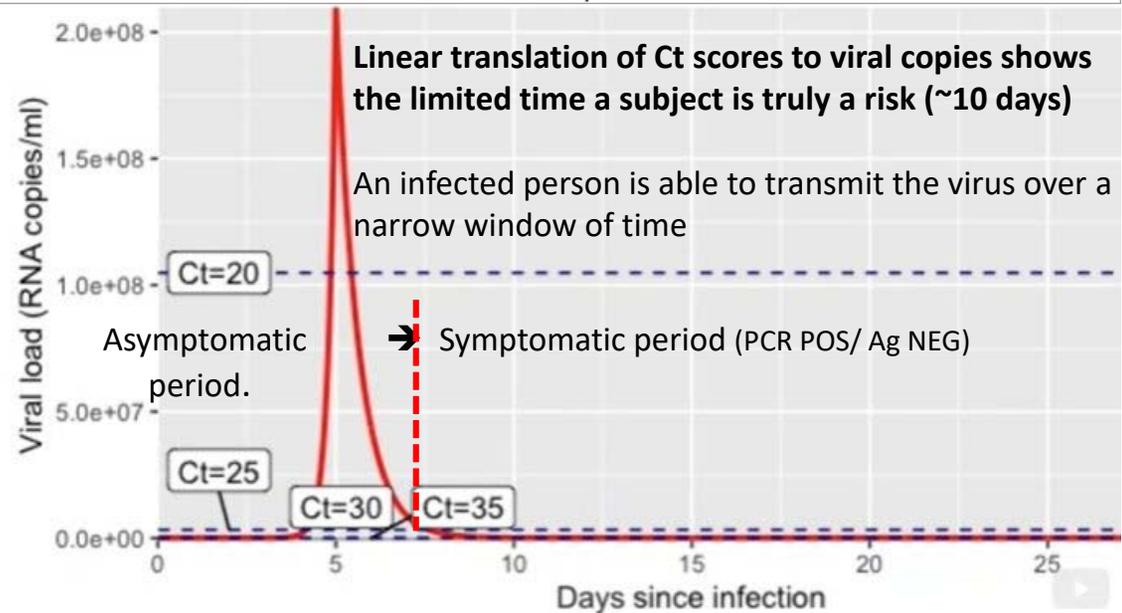
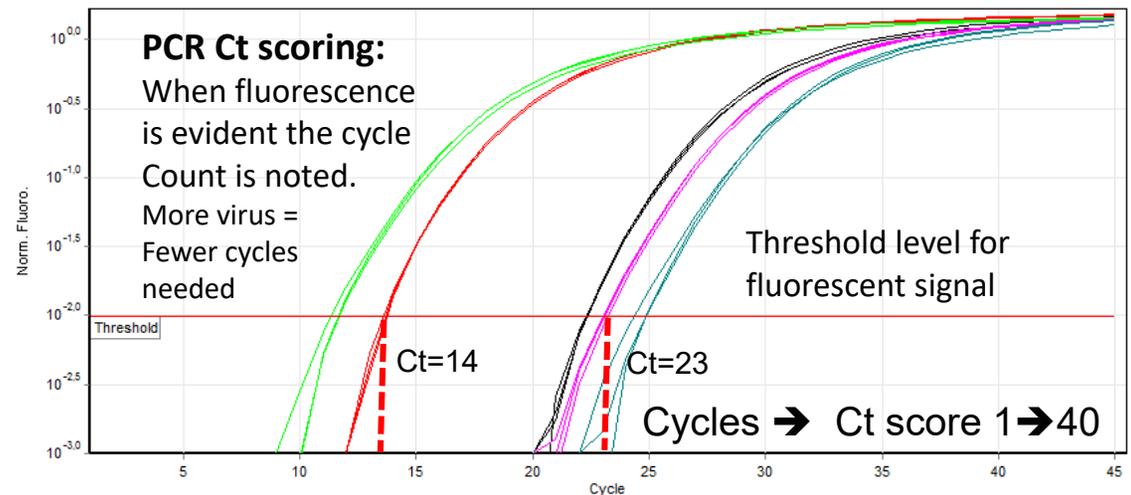
An “infected” person has Ct scores (PCR +) anywhere from 1 – 39 but an “**infectious**” person has Ct scores **LESS THAN 30** and generally around 20-25.

However: The actual “infectious period” is short

Ct scores converted to actual viral copies of DNA (RNA for COVID-19) shows the window of “transmission” is actually quite small at only Day 3 - 8 from infection and this is generally within an asymptomatic time.

The peak is where viral copies are in such abundance that the immune system is overwhelmed and sheds virus to others.

<https://www.youtube.com/watch?v=li4RRiMUxa8>



Why Are We NOT Using the Antigen (Ag) Tests to Control COVID-19 Transmission?

Antigen Testing is a way to take advantage of the high viral expression and shedding seen in infected persons.

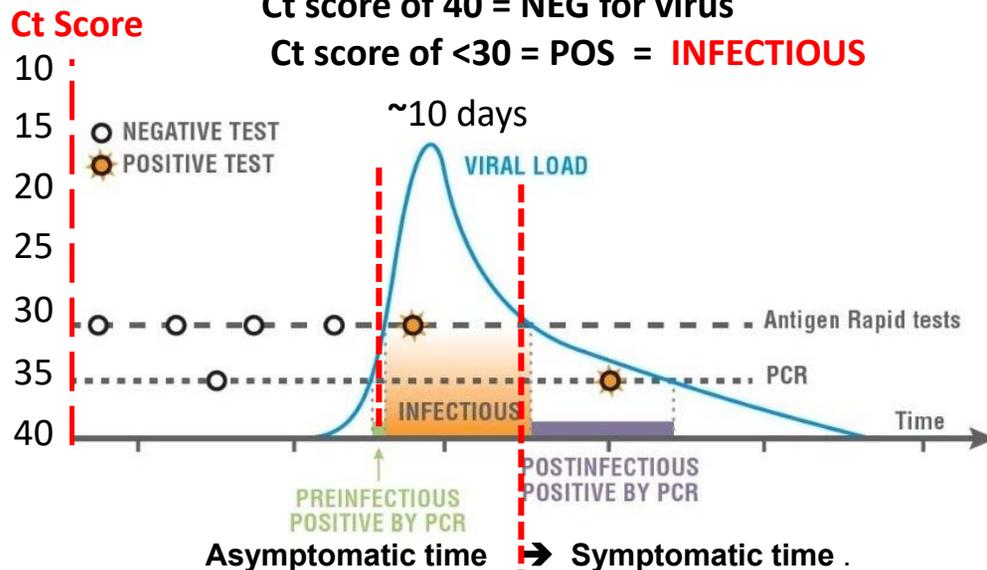
Over the Natural History of COVID-19 a person is likely PCR-POSITIVE for weeks, but Antigen Positivity is ONLY when there is a low Ct score (low = <30) which by the time-line in the graph below is potentially 3-8 days (~10 d). The key to stopping COVID-19 and to remove masking and social distancing needs is to identify people who are high viral counts (i.e., antigen expression).

While PCR POS tells us, you have the virus – **Ag POS means you are a danger to others for transmission/shedding.**

POS by PCR is weeks // POS by Ag is days

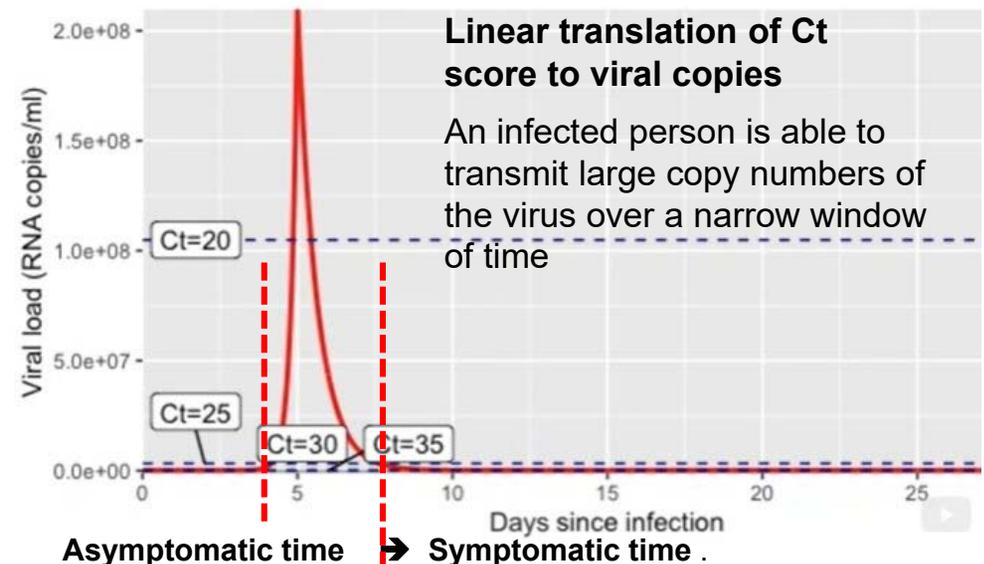
Ct score of 40 = NEG for virus

Ct score of <30 = POS = **INFECTIOUS**



https://primahometest.com/en/covid-19_antigen_rapid_test

Antigen POS is only a few days



<https://www.youtube.com/watch?v=li4RRiMUxa8>

FDA Authorized COVID-19 Antigen Tests

FDA-authorized Antigen Tests are available without a prescription. There are kits that require taking a sample and sending the sample to a lab but the clear advantage of a test done daily at home cannot be minimized.

These kits include the attribute "DTC" (for direct-to-consumer home collection tests) or "OTC" (for over-the-counter at-home tests). Two recently given EUA status and are applicable to "At Home" use are:

03/31/2021	Quidel Corporation	QuickVue At-Home OTC COVID-19 Test 03/31/2021	Lateral Flow, Visual Read, Over the Counter (OTC) Home Testing, Serial Screening	Home, H, M, W	HCP, Individuals, IFU, IFU (Home Test)
03/31/2021	Abbott Diagnostics Scarborough, Inc.	BinaxNOW COVID-19 Ag Card 2 Home Test 03/31/2021	Lateral Flow, Visual Read, Over the Counter (OTC) Home Testing, Telehealth Proctor Supervised, Serial Screening	Home, H, M, W	HCP, Individuals, IFU, IFU (Home Test)

<https://www.fda.gov/media/147247/download> , and; <https://www.fda.gov/media/147256/download>; resp

Point-of-care home kits from Ellume, Abbott, Cue, Quidel and Lucira are hitting the market in 2021. They will be available on drugstore and grocery store shelves. Results are delivered in about 15 minutes on a device the size of a credit card or results are delivered on a paper test strip that changes color in 10 minutes, which is like a home pregnancy test. **The costs will vary but likely a test will be between \$30-\$50 each.**

The Cue and Lucira tests use a newer molecular technology called isothermal amplification that is similar to PCR. Like PCR, it works by copying the virus's genetic material until there are detectable levels.

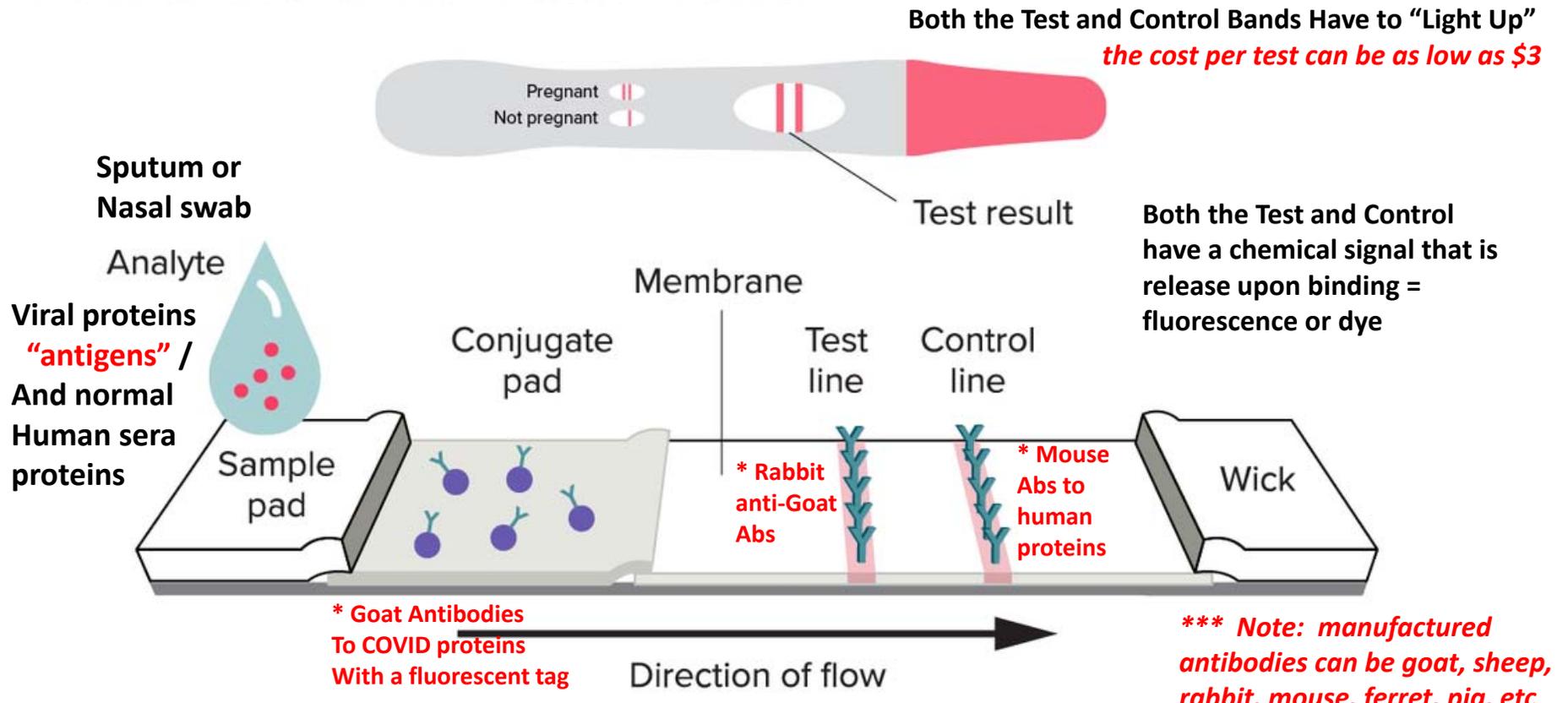
<https://www.fda.gov/consumers/consumer-updates/coronavirus-disease-2019-testing-basics>

<https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-antigen-diagnostic-tests-sars-cov-2>

What Does An Antigen Test Look Like?

The process uses *manufactured antibodies* tagged with a fluorescent or chemical dye

How a lateral flow test works



SOURCE: D.R. HRISTOV ET AL / SENSORS 2019

<https://www.smithsonianmag.com/innovation/scientists-are-racing-to-develop-paper-based-tests-for-covid-19-180975640/>

Comparing FDA Authorized COVID-19 Antigen Tests

Ellume COVID-19 Home Test

- Where/when to find it:** Sold over the counter at pharmacies and retail stores. Distribution is expected to start this spring.
- Type of test:** Antigen
- Does it require a prescription?** No
- Cost:** About \$30
- Who can use it:** People with or without coronavirus symptoms as young as 2 years old
- How long to get results:** 15-20 minutes, delivered via a smartphone app
- You need to know:** Results are more likely to be accurate if you have symptoms.

It must be remembered the PCR test is the “Gold Standard” because it finds any level of virus ...but that represents anywhere on the natural history.

Ct scores <30 are what we want to know, and antigen tests find individuals with high levels RAPIDLY.

Abbott BinaxNOW COVID-19 Antigen Self Test

- Where/when to find it:** Sold over the counter at pharmacies and retail stores. Distribution is expected to start in spring or summer.
- Type of test:** Antigen
- Does it require a prescription?** No
- Cost:** The company hasn't announced a price, but said in a press release it will be “priced affordably — similar to other OTC tests.”
- Who can use it:** People with or without coronavirus symptoms as young as 2 years old.
- How long to get results:** After 15 minutes, delivered on a small plastic card that has either one or two lines
- You need to know:** Results are more likely to be accurate if you have symptoms; To increase accuracy, the instructions call for users to administer two tests over three days, at least 36 hours apart.

Antigen Testing Summary

It is critical to understand how we can utilize Antigen Tests to avoid transmission of SARS-CoV-2

PCR is typically reporting only POS or NEG outcomes from testing but Ct scores (the number of duplications required to get a fluorescent signal) reveals a narrow band of time post infection where the subject expresses COVID-19 in excessive numbers that can infect others.

Knowing one has a high expression allows for quarantine and isolation over a 10 day period while “INFECTIOUS” and not over the 28+ days of “INFECTED” . This allows for commerce, schooling and social interactions to carry on with lower risk of transmission – not zero – but significantly less intrusion and risk.

The test of a sputum sample daily (or every other day) at a cost of \$1 -\$5 is affordable and far less costly to the economy and social structures than blanket PCR POS isolation practices.

THE KEYS are: **LOW COST MANUFACTURE** of the ANTIBODIES, SUFFICIENT RAW MATERIALS and a funded **SUPPLY CHAIN, FULL DISTRIBUTION of the TESTS** and **RIGOROUS ADHDERENCE** by INDIVIDUALS WITH Ct SCORE DENOTING a **REQUIREMENT TO QUARANTINE**

- One other point may be to have variant-specific antibodies that can be flexible or combined into a test.