Testing for COVID-19 and HIV:

It is what it is.

Bernard M Branson MD
March 24, 2021
Disclaimer

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Use of Brand Names

- This presentation may refer to individual tests by brand name for the purposes of identification and clarity.

- No endorsement of any specific test is intended.
Session Objectives

- Understand the fundamentals of laboratory tests for SARS-CoV-2.
- Appreciate the role for serology tests in identifying exposure to SARS-CoV-2.
- Review new developments in HIV tests and their utility for a new diagnostic algorithm.
- Describe how similar parameters affect the accuracy of tests for SARS-CoV-2 and HIV.
Poll Question 1: Which COVID-19 tests have received FDA-approval?

A. PCR tests
B. Antigen tests
C. Antibody tests
D. Home tests
E. All of the above
F. None of the above
FDA Regulation of Devices: a Quick Primer

- **License**: Biologics (tests for blood screening)
- **Approval**: high-risk devices (HIV Ag, Ab, RNA tests)
  - Pre-market approval application
- **Clearance**: most diagnostic tests
  - 510(k) application
- **Emergency Use Authorization**: not approval
A few more regulations apply...

- **CLIA**: Clinical Laboratory Improvement Amendments (of 1988)
  - Part of CMS (Center for Medicare and Medicaid Services) classifies devices and certifies laboratories to perform tests based on complexity:
    - High
    - Moderate
    - Waived (Home tests are automatically waived)

- **LDTs**: Laboratory-developed tests (*FDA requirements suspended*)
  - For use only by laboratory that developed the assay
  - Can be for novel assay (SARS-CoV-2) or one for which assays exist (Vitamin D)
# How Confident in Results? It Depends.

<table>
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<th>Test Type</th>
<th>Method</th>
<th>No. of Specimens</th>
<th>Sensitivity/PPA (95% CI)</th>
<th>Specificity/NPA (95% CI)</th>
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<td>35</td>
<td>67</td>
<td>97 (85-99)</td>
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Current Status, SARS-CoV-2 Tests

- **336 Emergency Use Authorizations**
  - **RT-PCR:** >200
    - 18 for saliva specimens
    - 29 home swab collection systems
    - 15 COVID-19/Influenza A-B multiplex
  - **Antigen:** 16
    - 8 High or moderate complexity lab assays
    - 7 rapid, waived complexity
    - 1 rapid home test, instrument read
  - **Antibody:** 65
Initial Steps: RT-PCR for SARS CoV-2 RNA

205 patients, 1070 specimens
- BAL 14/15 (93%)
- NP swab 5/8 (63%)
- Throat swab 126/398 (32%)
- Sputum 75/104 (72%)
- Saliva
- Feces 44/153 (29%)

Wong et al, JAMA March 2020

Extract RNA from cellular debris, eliminate DNA
Use reverse transcriptase to form complementary DNA
Real time DNA PCR

Initial Steps:
- Tissue sample
- RNA extraction
- cDNA formation
- Real-time PCR amplification
RNA extraction
Heat to denature cDNA to create two single DNA strands

Reverse Transcriptase makes cDNA from viral RNA

Lower temp, primers bind to 3’ and 5’ ends of single-stranded DNA

Add DNA polymerase to create 2 new cDNA molecules

Repeat “thermocycle”
Chain Reaction: Exponential Amplification

Number of copies in 1st cycle determined by number of copies in specimen

1st cycle: $2^2 = 4$ copies
2nd cycle: $2^3 = 8$ copies
3rd cycle: $2^4 = 16$ copies
4th cycle: $2^5 = 32$ copies
30th cycle: $2^{31} = 1$ billion copies

“Cycle threshold” for negative specimen

2$^{21} = 1$ million copies
2$^{31} = 2$ billion copies
## Comparative Analytical Sensitivity
### FDA Performance Panel

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<th>Product LOD (NDU/mL*)</th>
<th>Developer</th>
<th>Test</th>
<th>Time</th>
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<td>Perkin Elmer</td>
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<td>Quidel Corporation</td>
<td>Lyra Direct SARS-CoV-2 Assay</td>
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*NAAT-detectable units/mL

- FDA.gov/medical-devices as of 9/15/2020
Poll Question 2:

Compare saliva specimens with nasal swabs.

Which statement is incorrect:

A. Saliva is less accurate than nasal swabs.
B. Saliva is easier to collect than nasal swabs.
C. Virus is detected longer in saliva than in nasal swabs.
D. Saliva specimens require special preservatives for RT-PCR.
E. RT-PCR is more expensive with saliva specimens because of special handling and extraction procedures.
Saliva Test: EUA for SalivaDirect Protocol

- EUA issued to Yale School of Public Health August 15, 2020
- Uses unprocessed saliva, collected into sterile urine cup or test tube
- No extraction step required
SalivaDirect Protocol for SARS-CoV-2 RT-PCR

- Eliminates need to collect NP swab, so no swab or transport medium
- Eliminates need for RNA extraction kit (supply issues)
- Validated for use with reagents, primers and instruments from several different diagnostics manufacturers – and counting
- Distributed free to individual laboratories
- Commercial laboratories must obtain a license (free) that negotiates retail price they can charge
Paired specimens from 70 hospitalized patients with NP swabs positive for SARS-CoV-2 on hospital admission

-Wyllie et al, Yale University
Simplified, sensitive, economical SalivaDirect method

Total minimum reagent cost per sample: $1.29 - $4.37
From CDC: Transmission electron micrograph of isolate from first U.S. case of COVID-19

Virus particles (blue) with cross-section through viral genome (black dots)
SARS-CoV-2 viral antigens and RNA

- CDC Flu SARS-CoV-2 Multiplex (Flu SC2)
  - SARS CoV-2: N gene
  - Influenza A: Matrix gene
  - Influenza B: NS2 gene
  - Internal Control: RNAse P
  - Positive Control: FluSC2PC

- SPIKE GLYCOPROTEIN (S)
- MEMBRANE PROTEIN (M)
- NUCLEOPROTEIN
- GENOMIC RNA
- N1, N2
- ENVELOPE SMALL MEMBRANE PROTEIN (E)
Testing strategies

- Symptomatic persons only ("revised" CDC guidelines)
- Test symptomatic persons and known contacts
- Test anyone on demand
- Test everyone twice a week (Saliva: University of Illinois)
- Focused testing after sentinel testing of sewage from specific locations (e.g., dorms – U of Arizona)
Test sensitivity is secondary to frequency and turnaround time for COVID-19 screening

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++

First release: 20 November 2020
Serial Testing Strategy – Congregate setting

The number of infections identified and quarantined depends more on the frequency of the test than the test’s sensitivity.
RT-PCR vs Antigen tests

- RT-PCR is exquisitely sensitive for presence of viral material.

- Most tests report sensitivity compared with RT-PCR

- RT-PCR also detects viral transcripts (fragments) that cells produce in excess compared with infectious virions

- Infectious virus is rare at RT-PCR RNA values $<10^6$ copies/ml

- Cevik et al, Lancet Microbe 2021
Antigen vs RT-PCR tests

Antigen tests are visually read, antigen-antibody interactions.

Antigen “Sensitivity” = Positive Percent Agreement with RT-PCR

- 1098 Paired swabs from WI college students (5.2% overall prevalence)¹
  - 80% among 227 (21%) participants with one or more symptoms
  - 41% among 877 (77%) asymptomatic participants

- UK Oxford study
  - 79% when performed by lab professionals
  - 73% when performed by trained health care workers
  - 57% when performed by self-trained public using a protocol

¹MMWR Jan 29, 2021  ²Public Health England Nov 8, 2020
RT-PCR vs Antigen tests Limits

- No study identified infectious virus >9 days after onset of symptoms despite weeks of persistently positive RT-PCR.

- RT-PCR have limits of detection of $10^3$-$10^4$ copies/ml or lower, but infectious virus is rare at RT-PCR RNA values $<10^6$ copies/ml, a level that Antigen tests can achieve.

- Genetic variants might lead to false-negative RT-PCR if the mutation involves the part of the genome detected by the test.

- Cevik et al, Lancet Microbe 2021
The role for Antigen tests

- Antigen tests take 15-20 minutes, RT-PCR takes 4+ hours.
- Antigen tests are less expensive and suitable for POC.
- Antigens likely detect persons who are infectious, but might be false-negative in some cases.
- RT-PCR remains positive long after infectious virus is gone.
The role for Antigen tests

- Antigen tests make it possible to conduct repeated serial testing
  - often enough
  - deliver results fast enough
  - at costs low enough

  to make surveillance testing (dormitories, schools, nursing homes, job sites...) feasible.
COVID-19 Screening Strategies

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

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. Mina7,8,9* and Roy Parker4,6,10,2*†

First release: 20 November 2020
Ellume Home test for SARS-CoV-2 Antigen

Detects nucleocapsid antigen from nasal swabs
Ellume COVID-19 Home Test: FDA EUA December 15, 2020

- 15-minute fluorescent antigen test
- Testing app for iOS, Android
- Video and step-by-step instructions on app
- Battery operated analyzer connects with phone via Bluetooth
- Result appears on phone after 15 minutes
- Test result also reported to health department
- Email result optional
IMMEDIATE RELEASE

DOD Awards $231.8 Million Contract to Ellume USA LLC to Increase Domestic Production Capacity and Deliver COVID-19 Home Tests

FEB. 1, 2021
Poll question 3: Which statement is true about antibody tests?

A. A positive antibody test means a person has COVID-19.
B. A positive antibody test means a person is immune.
C. A positive antibody test provides insight into the prevalence of COVID-19 in a population.
D. Antibody tests help identify new mutant viral variants.
PCR vs Antibody tests

- PCR tests detect the presence of viral material, but cannot determine whether a person has been infected previously and recovered.

- Serology tests determine whether a person has been previously exposed to a pathogen

- Serology tests provide insight into the prevalence of a disease in the population by identifying those with specific antibodies
FDA Regulation: Lessons from HIV testing

- Antibody tests came first.
  - Intended for screening the blood supply so...
  - “High risk” designation by FDA (= PMA); CBER vs CDRH
  - First quantitative HIV-1 viral load monitoring test approved in 1996
  - First HIV-1 RNA diagnostic test (qualitative) in 2006

- FDA (CBER & CDRH) proposed “down-classification” of HIV and HCV tests to class II (recommended by Advisory Committee in March 2018) – public comment spring 2020
Lessons from HIV testing?

- FDA required COVID-19 LDTs to obtain Emergency Use Authorizations, then
- FDA granted blanket EUAs, first to LDT PCRs
- FDA first granted waiver from EUAs for antibody tests
  - CLIA waiver also OK’d
- FDA issued EUAs for several antibody tests, then later rescinded them and required EUAs for the others
- FDA has rescinded 254 EUAs for COVID-19 tests – so far.
Types of SARS CoV-2 antibody tests

- Lateral flow assays (LFAs)  
  Rapid, point of care

- ELISA  
  Chemiluminescent, electrochemiluminescent  
  Potential for high throughput

- Neutralizing antibody assays  
  Serial dilutions of serum added to viral cultures to look for areas of inhibition
COVID-19: Dynamic Changes in IgG Levels

- 285 patients with COVID-19:
  - 100% tested positive within 19 days after symptom onset
  - Seroconversion for IgG and IgM occurred simultaneously or sequentially

- Long et al, Nature Medicine 2020
Antibody tests: HIV versus COVID-19

- Positive HIV antibody tests indicate active HIV infection

- Positive COVID-19 antibody tests:
  - Single test has low positive predictive value in most populations
  - Indicative of past exposure, not necessarily active infection
  - Unknown whether antibodies indicate immune protection
  - If antibodies confer immunity, not certain how long it will persist
Interpreting screening test results

For a laboratory test:

**Sensitivity**: Probability test=positive if patient=positive

**Specificity**: Probability test=negative if patient=negative

For COVID tests:

**Positive Percent Agreement**: Probability test2=positive if test1=positive

**Negative Percent Agreement**: Probability test2=negative if test1=negative

**Predictive value**:

Probability patient=positive if test=positive

Probability patient=negative if test=negative
# Specificity of SARS CoV-2 antibody tests

## Specificity in 108 blood donor plasma specimens collected before July 2018

<table>
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<tr>
<th>Assay</th>
<th>Immunochromatographic Lateral Flow Assays</th>
<th>ELISAs</th>
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<td>Total N</td>
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<tr>
<td><strong>Mean</strong></td>
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</table>
Poll question: What happens with results of tests when the prevalence of disease is low?

A. The number of false-positive tests is higher.
B. There is a higher likelihood that a positive result is a false-positive.
C. Chance of false-positive results are much reduced.
D. Nothing. False-positive results are unaffected by prevalence.
Example: Test 10,000 persons
Test Specificity = 94.2% (58/1000)

SARS-CoV-2 prevalence = 10.5%

True positive: 1050  False positive: 580

Positive predictive value: 1050/1630 = 65%
Example Continued: Test 10,000 persons

Test Specificity = 94.2% (58/1000)

SARS-CoV-2 positivity = 10%
True positive: 1050 False positive: 580
Positive predictive value: 1050/1630 = 65%

SARS-CoV-2 positivity = 1.3%
True positive: 130 False positive: 580
Positive predictive value: 130/710 = 18%
Continued Example: Test 10,000 persons

Test Specificity = 94.2% (58/1000)

SARS-CoV-2 positivity = 1.3%
True positive: 130  False positive: 580
Positive predictive value: 130/710 = 18%

Test Specificity = 98.5% (15/1000)
SARS-CoV-2 positivity = 1.3%
True positive: 130  False positive: 150
Positive predictive value: 130/280 = 46%
HIV-1: viral antigens and RNA

- gp120
- gp 41
- p24
- RNA
- pol: Protease, RT, polymerase, integrase
HIV-1/HIV-2 antigen/antibody immunoassay

(+)

HIV-1 antibodies detected

HIV-2 antibodies detected

(-)

HIV-1 (-) or indeterminate

HIV-2 (-) or indeterminate

NAT: nucleic acid test

HIV-1/2 antibody differentiation immunoassay

(+)

HIV-1 (+)

HIV-2 (-)

HIV-1 antibodies detected

HIV-2 antibodies detected

(-)

HIV-1 (-)

HIV-2 (+)

HIV antibodies detected

HIV-1 NAT

HIV-1 NAT (+)

Acute HIV-1 infection

HIV-1 NAT (-)

Negative for HIV-1

(+): reactive test result
(-): non-reactive test result
FDA Approved November 20, 2020

NOW AVAILABLE

Aptima® HIV-1 Quant Dx Assay

Diagnostic Claim for HIV-1 Quant Assay

The FIRST and ONLY dual-claim assay to confirm HIV-1 infection and measure viral load for optimal patient management.
Aptima HIV-1 Quantitative Dual Claim

- **Diagnosis:**
  - Serum or plasma

- **Monitoring:**
  - Plasma only
Plasma/Serum Comparative Performance Aptima HIV-1 RNA QT Assay

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Source: FL Public Health Lab validation (with permission)
### Plasma/Serum Comparative Performance Aptima HIV-1 RNA QT Assay

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<th>Plasma</th>
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Source: FL Public Health Lab validation (with permission)
HIV-1/2 antigen/antibody immunoassay (review)

HIV-1 RNA viral load

Detectable

(99.6%)

Treat

Undetectable

HIV-1/2 antibody differentiation immunoassay

HIV-1 (+) HIV-2 (-)

HIV-1 (-) HIV-2 (+)

HIV-1 (+) HIV-2 (+)

HIV-1 (-) or ind HIV-2 (-) or ind

HIV infected

2nd Ag/Ab assay

Add’l NAT

(+) (-)

Uninfected

Negative for HIV-1 and HIV-2 antibodies and p24 Ag
“Point-of-Care” Nucleic Acid Tests

- Xpert HIV-1 viral load
  - 1 ml plasma
  - Results in 90 minutes
  - LOD 32 copies/mL
  - CE-marked December 2014

*Not yet available in U.S.*
Summary

- Regulation of COVID-19 tests is substantially different than that for HIV tests – and it shows!
- RNA & viral load will play an increasingly important role in HIV diagnosis
- Most covid-19 diagnoses depend on PCR testing of NP swabs, but saliva specimens offer an attractive alternative
- Antibody testing will help to identify persons who have already been infected.
- Serial antigen testing might play a useful role in limiting COVID-19 transmission
OHIO STATE’S COVID-19 BREATHALYZER TEST STILL AWAITING FDA APPROVAL

January 25, 2021
Questions?