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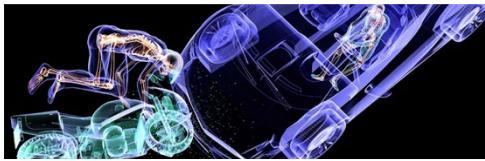
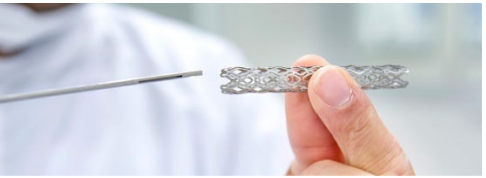

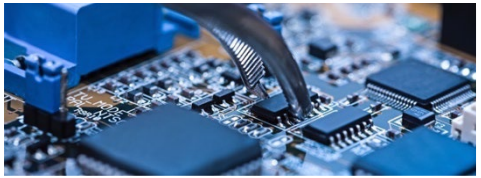


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COVID-19 Testing Fundamentals, Regulation and Legal Landscape

Christie Bergerson, Ph.D.
Jianlin Song, Esq.

November 16, 2022

Disclaimer

Any recommendations are made for your consideration given our understanding of the most current information.

Examples provided in this presentation are for discussion purposes only and are not applicable to specific circumstances without additional consideration.

The state of the science of SARS-CoV-2 and COVID-19 is rapidly changing, and some scientific literature has not been peer reviewed before publication.

Presenters

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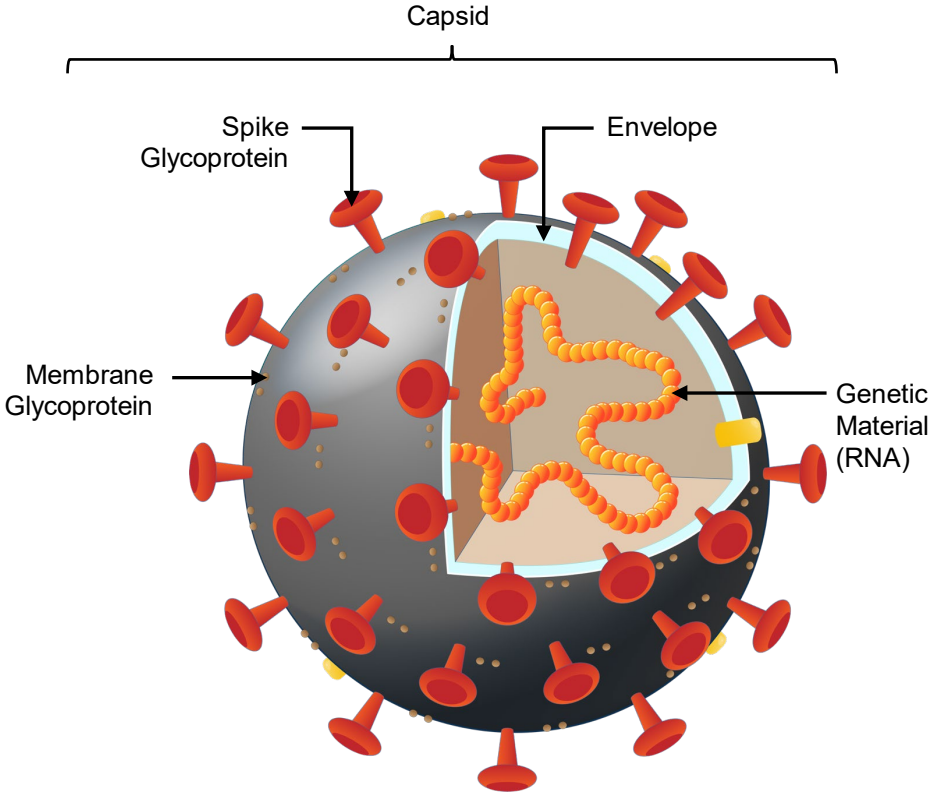
Background

Coronavirus Basics

- A virus consists of genetic material contained within a protein shell called a capsid.
- In some viruses, the protein shell is enclosed in a membrane called an envelope.
- Coronavirus is an enveloped RNA virus that has spike proteins in its capsid that resemble a crown.
- The virus that causes COVID-19 is called SARS-CoV-2.



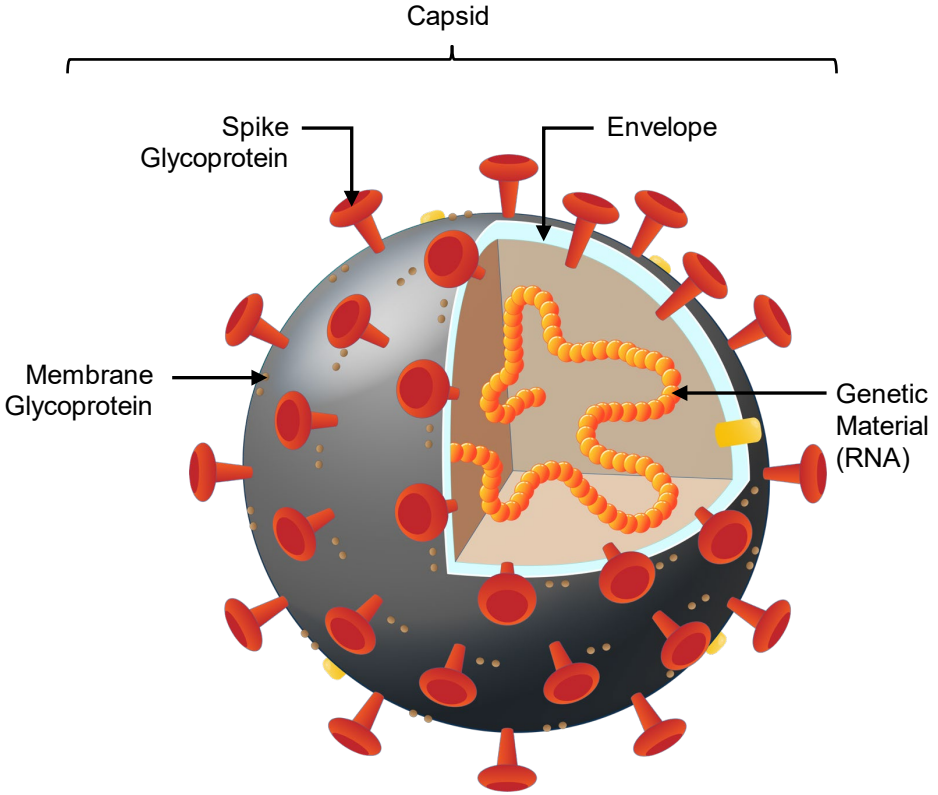
Testing Basics

Diagnostic Tests
Is the virus present?

- Molecular Tests (NAAT) Detect RNA
- Antigen Tests Detect Capsid Proteins
- Viral Culture Detects Virus Infectivity

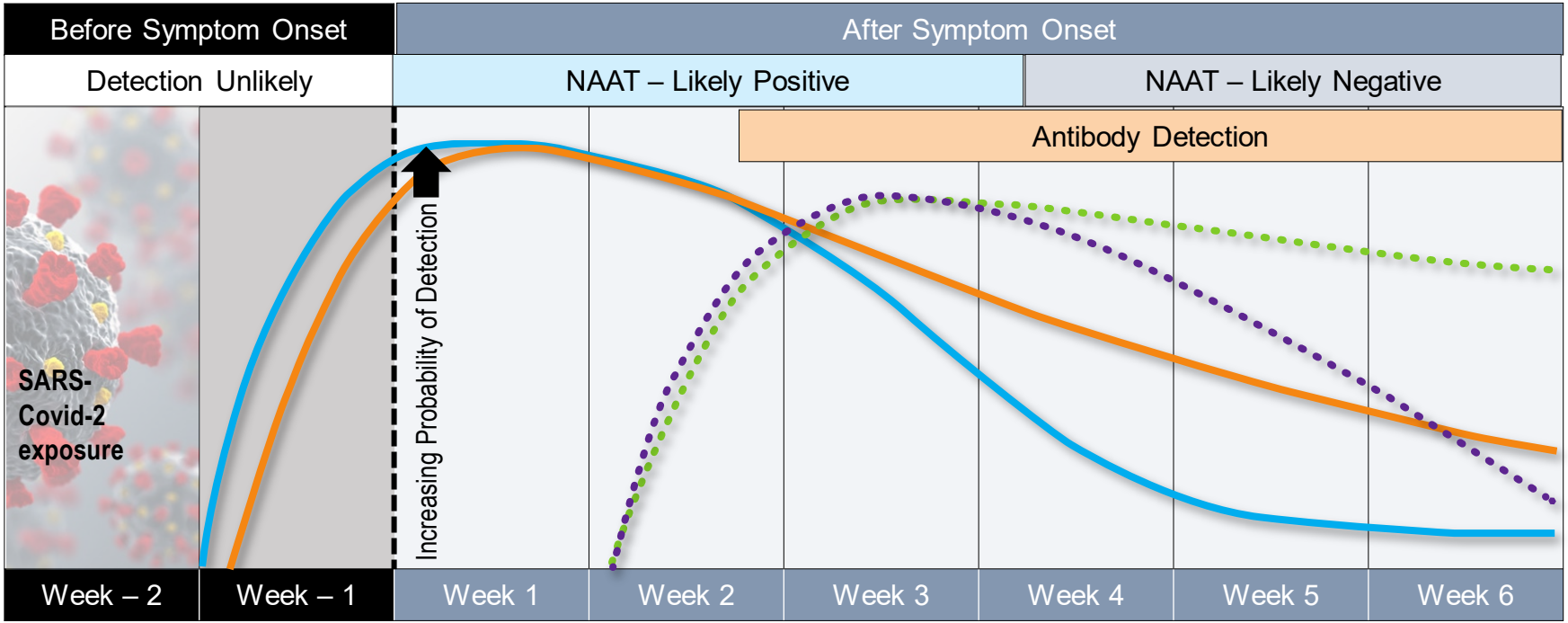
Serological Tests
Were you previously infected with the virus?

- Serological Tests Detect Antibodies against the Virus



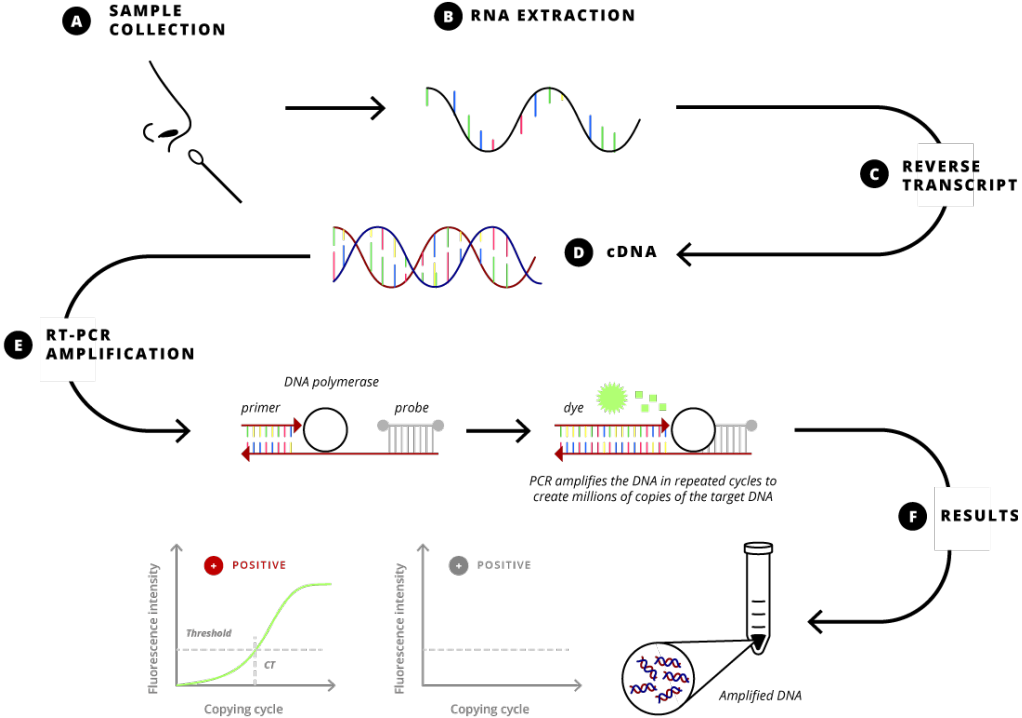
NAAT = Nucleic Acid Amplification Test

Different Tests for Different Purposes

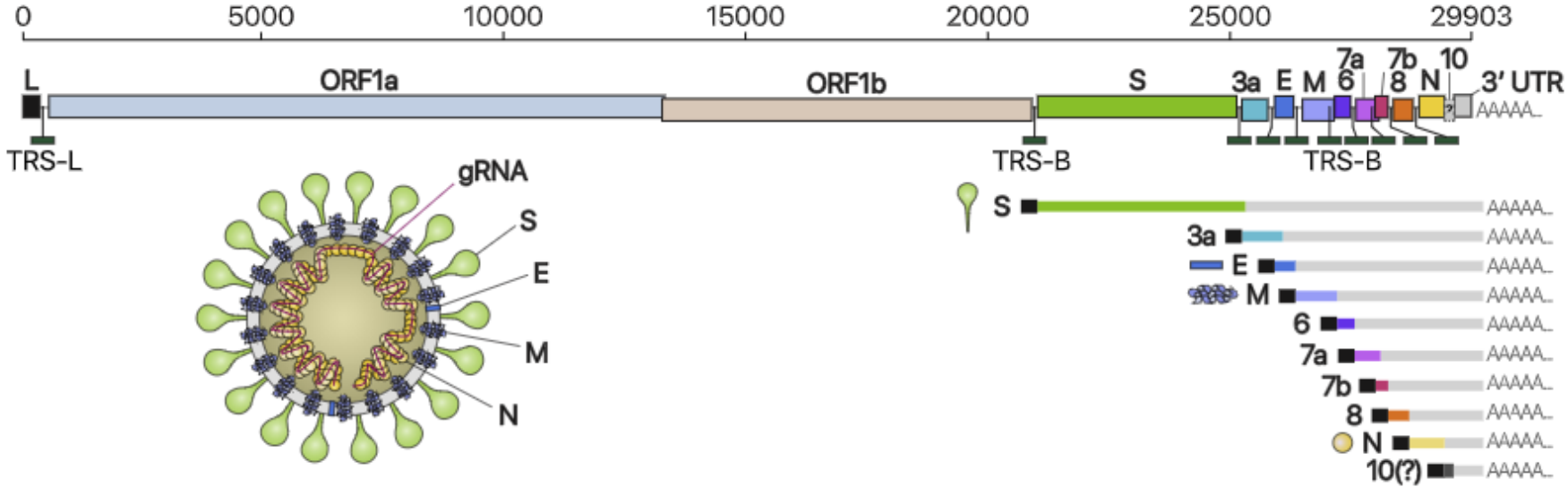


Molecular Tests/NAAT – How Do They Work?

- Detection mechanism
  - Nucleic acid amplification
- Sample types
  - Nasal swabs (nasopharyngeal, mid-turbinate, anterior nares)
  - Saliva
  - Bronchoalveolar lavage fluid
  - Oropharyngeal
- Target analytes
  - Viral RNA



SARS-CoV-2 Genetic Structure



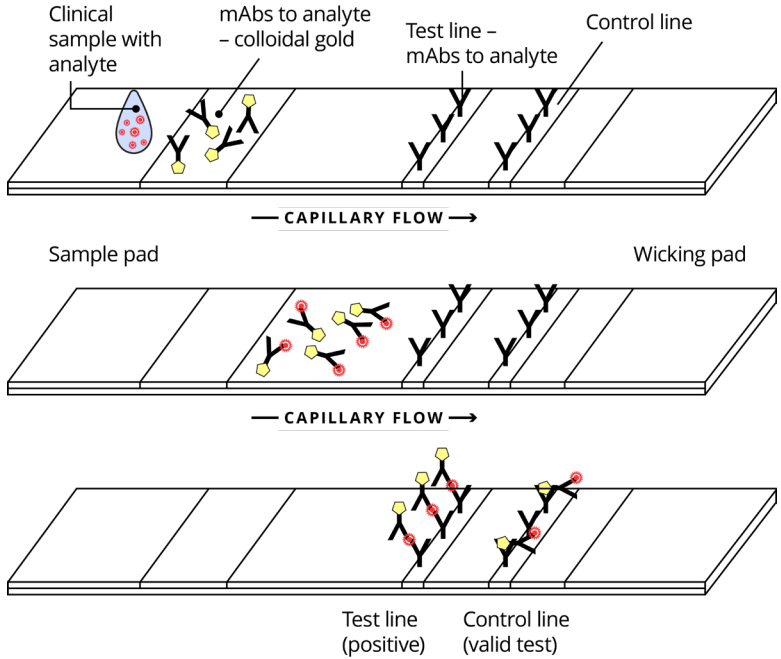
Kim D, Lee JY, Yang JS, Kim JW, Kim VN, Chang H. The Architecture of SARS-CoV-2 Transcriptome. Cell. 2020 May 14;181(4):914-921.e10.

Molecular Tests/NAATs - Pros & Cons

Pros	Cons
• Gold standard for nucleic acid detection • Can be very sensitive • Can be multiplexed to detect multiple genes at once	• Test complexity often requires laboratory and skilled workers • Relatively Expensive • Relatively slow • False negatives can occur with mutations

Antigen Tests – How Do They Work?

- Detection Mechanism
  - Sandwich immunoassay
- Sample Types
  - Nasal swabs (NP, mid-turbinate, anterior nares)
  - Saliva
  - Bronchoalveolar lavage fluid
- Target Analytes
  - Viral proteins (e.g., S or N)

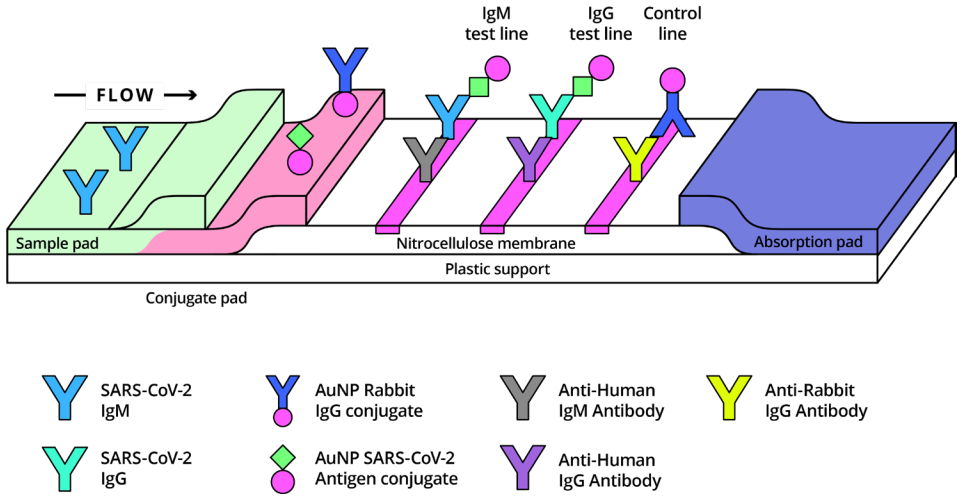


Antigen Tests - Pros & Cons

Pros	Cons
• Format well-suited to point-of-care and at-home settings • Can be rapid • Can be easy to use • Relatively inexpensive	• Often less sensitive than NAATs (more false negatives) • Often less specific than NAATs (more false positives) • Can be impacted by mutations

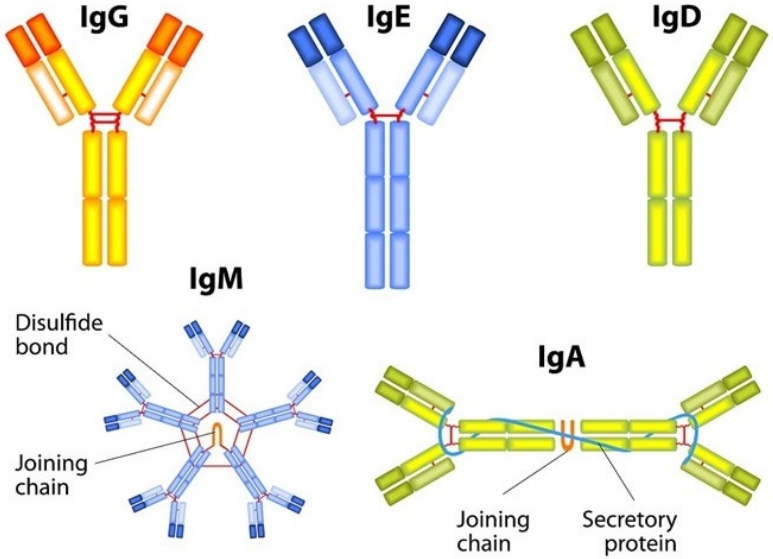
Serological Tests – How Do They Work?

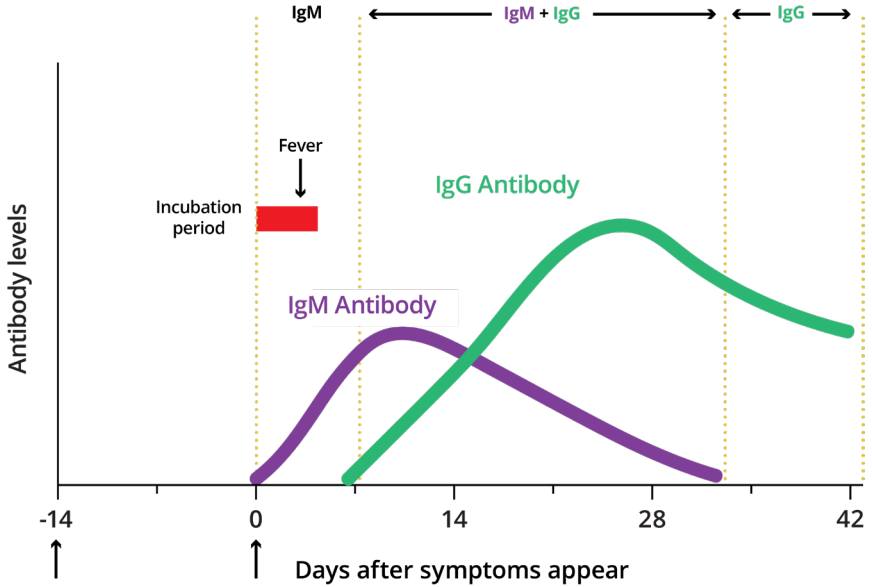
- Detection mechanism
  - Immunoassay
- Sample types
  - Whole blood
  - Serum
  - Plasma
- Target analytes
  - Anti-SARS-CoV-2 antibodies



Peng et al; Appl. Phys. Lett. 117, 120601 (2020)

Not All Antibodies Are The Same: IgM v. IgG



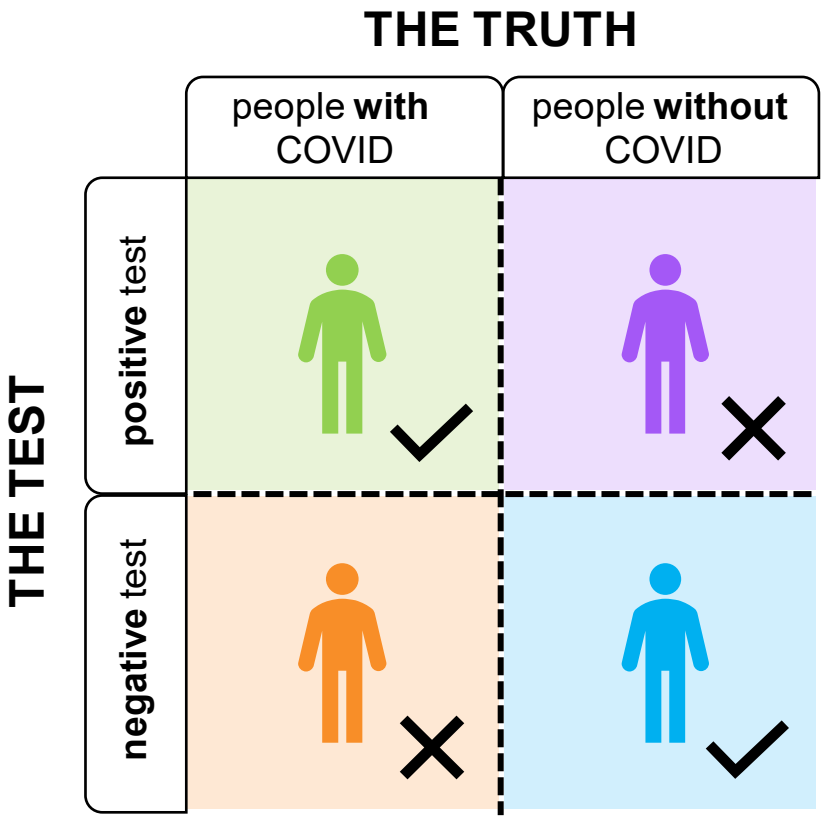


Serological Tests - Pros & Cons

Pros	Cons
• Rapid format well-suited to point-of-care and at-home settings • Can be easy to use • Relatively inexpensive	• Does not differentiate between active and past infection • A negative test does not rule out prior infection • Currently not FDA authorized to measure immunity

Types of Errors

- False Positives
  - Test measures the presence of a similar analyte, instead of the target analyte.
  - Interfering substance causes signal.
- False Negatives
  - Analyte concentration is below the test's limit of detection.
  - Interfering substance prevents detection of the analyte.



Testing Steps

Specimen Collection

- Quality Considerations
  - Amount of sample
  - Type of sample
  - Physiological differences
- User errors
  - Mislabeled
  - Improper sample collection

Specimen Transport

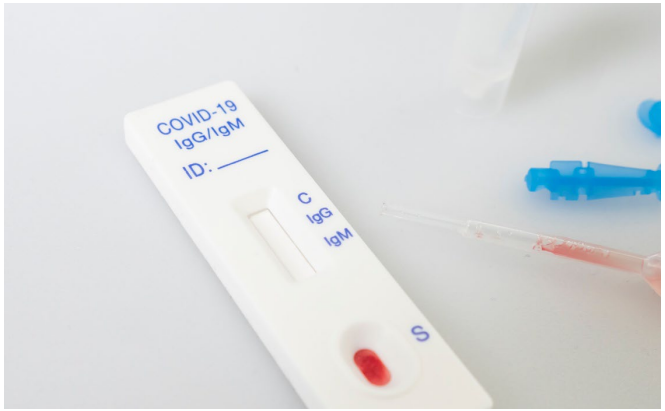
- Environmental Conditions
  - Temperature excursions
  - Degradation over time
- Physical Handling
  - Vial leaking/breaking
  - Loss of sample
  - Contamination

Sample Preparation

- User errors
  - Labelling and entering into tracking system
  - Workspace contamination
  - Insufficient sample added
  - Manual vs. automated
- Reagent issues
  - Manufacturing errors
  - Lot to lot variability
  - Contamination
  - Reagent degradation over time
  - Improper storage of reagents

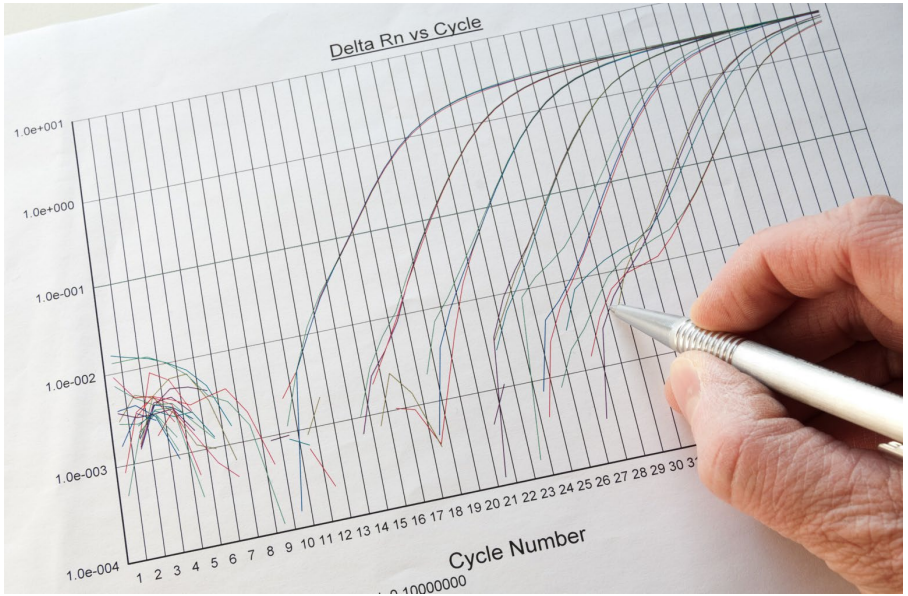
Conduct Test

- User errors
  - Manual vs. automated
  - Mislabeling
  - Workspace contamination
- Instrument issues
  - Malfunction
  - Out of calibration



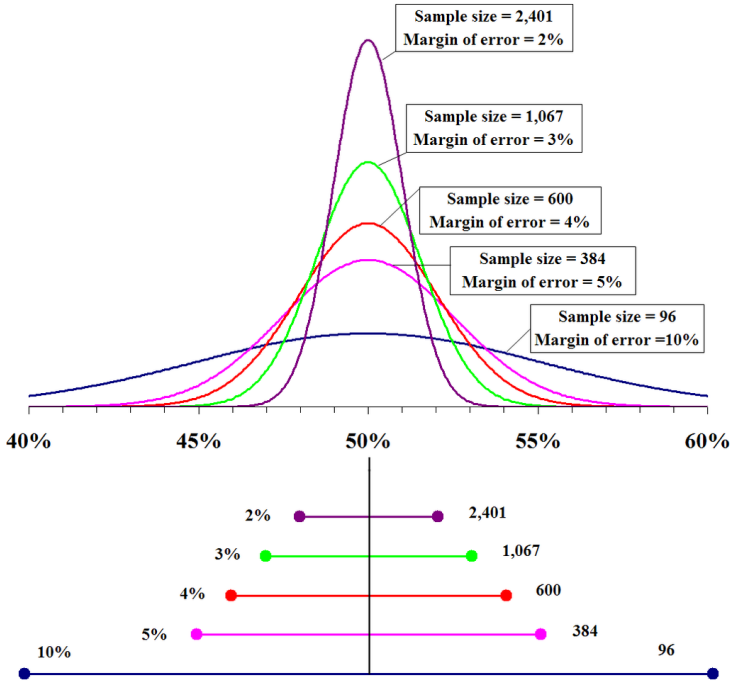
Reporting Results

- Data interpretation
  - Multiple targets
  - Valid positive and negative controls
- Reporting to health care provider
  - Mislabeling
  - Interpretation when diagnostic test does not correlate with clinical history



Interpreting Accuracy from Clinical Data

- Sample size
- Confidence intervals
- Performance in subpopulations



DTC v. OTC | Home Collection v. Home Test

DTC
(Direct to Consumer)

Home Collection

OTC
(Over the Counter)

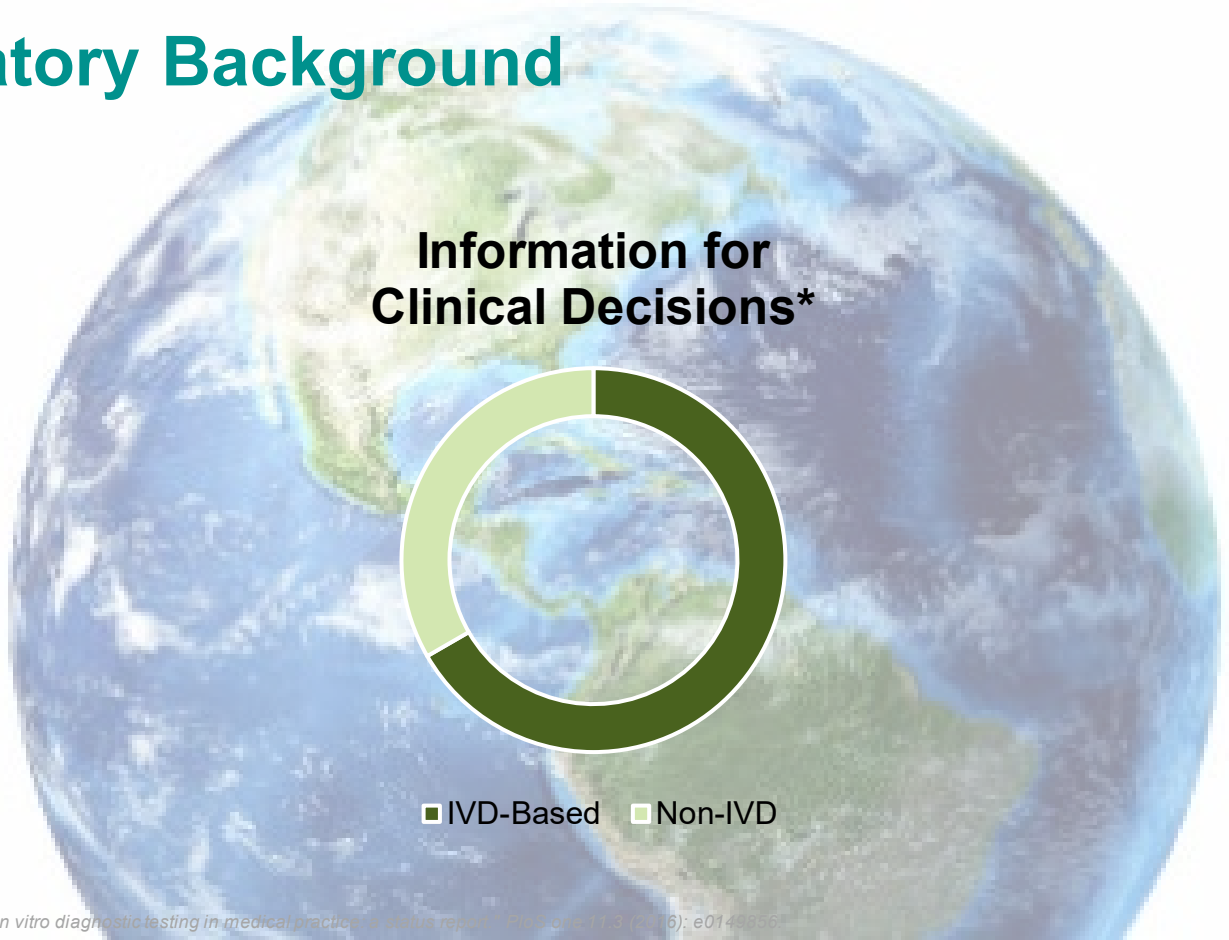
Home Test

In Summary…

- False results have a variety of sources
  - Patient specific factors
  - User errors (in the lab and at home)
  - Viral variants escaping detection
- Interpretation of COVID-19 data should be undertaken with a detailed understanding of key parameters, including testing methods and sampling protocols.
- The science on COVID-19 continues to evolve but is much more advanced than at the beginning of the pandemic. The information presented today represents our current knowledge.

COVID-19 Regulatory History

Regulatory Background



Rohr, Ulrich-Peter, et al. "The value of in vitro diagnostic testing in medical practice: a status report." PloS one 11.3 (2016): e0149856.

FDA Medical Device Regulation

- All medical devices on market must go through FDA and be cleared/approved/authorized
  - Including COVID-19 diagnostic tests

- Several different pathways depends upon classification and risk
  - Class III devices: PMA – Highest risk category, independent demonstration of safety and effectiveness
  - Class II devices: Comparative analysis
  - Traditional 510(k) – Substantial Equivalence, comparison to legally marketed predicate (same intended use, same/similar technological characteristics)
  - De Novo 510(k) – New or different, no predicate available but still can be class II
  - Class I devices: general regulatory controls (common to all devices)
  - EUA – Emergencies Only (Benefit-Risk in context of public health emergency)

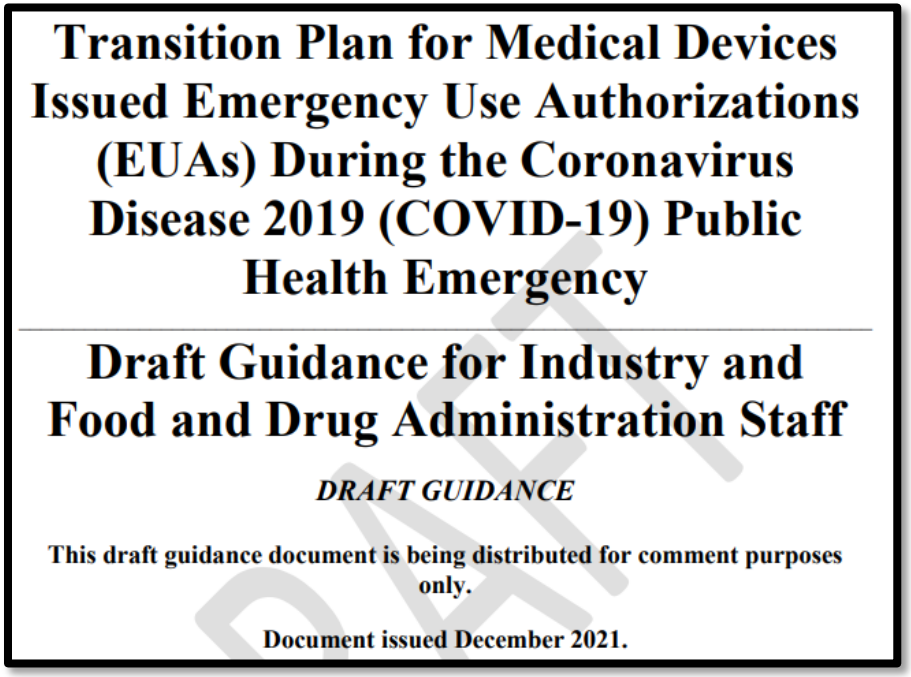
- To be under review is to be vetted by the FDA's experts
  - Takes time
  - You do have some control
    - Submission organization
    - Prompt answers to questions

Background: Regulatory Environment

- FDA's Emergency Use Authorization (EUA) Process
  - Enacted for COVID-19 pandemic
    - Used for authorizing IVD tests, PPE, vaccines, etc.
    - Goal communicated to be speed of addressing public need
- Traditional Submissions Encouraged
  - EUA still in effect though only prioritized applications are being reviewed
  - 510(k) and De Novo encouraged by FDA where appropriate.

Pathway Transition

- EUA ⟹ 510(k) or De Novo
  - Developers expected to comply with all parts of QMS regulations
- Transition Implementation Plan
  - Amount of Product On-Market
  - Actions if granted/cleared for market
  - Actions if rejected



Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency

Draft Guidance for Industry and Food and Drug Administration Staff

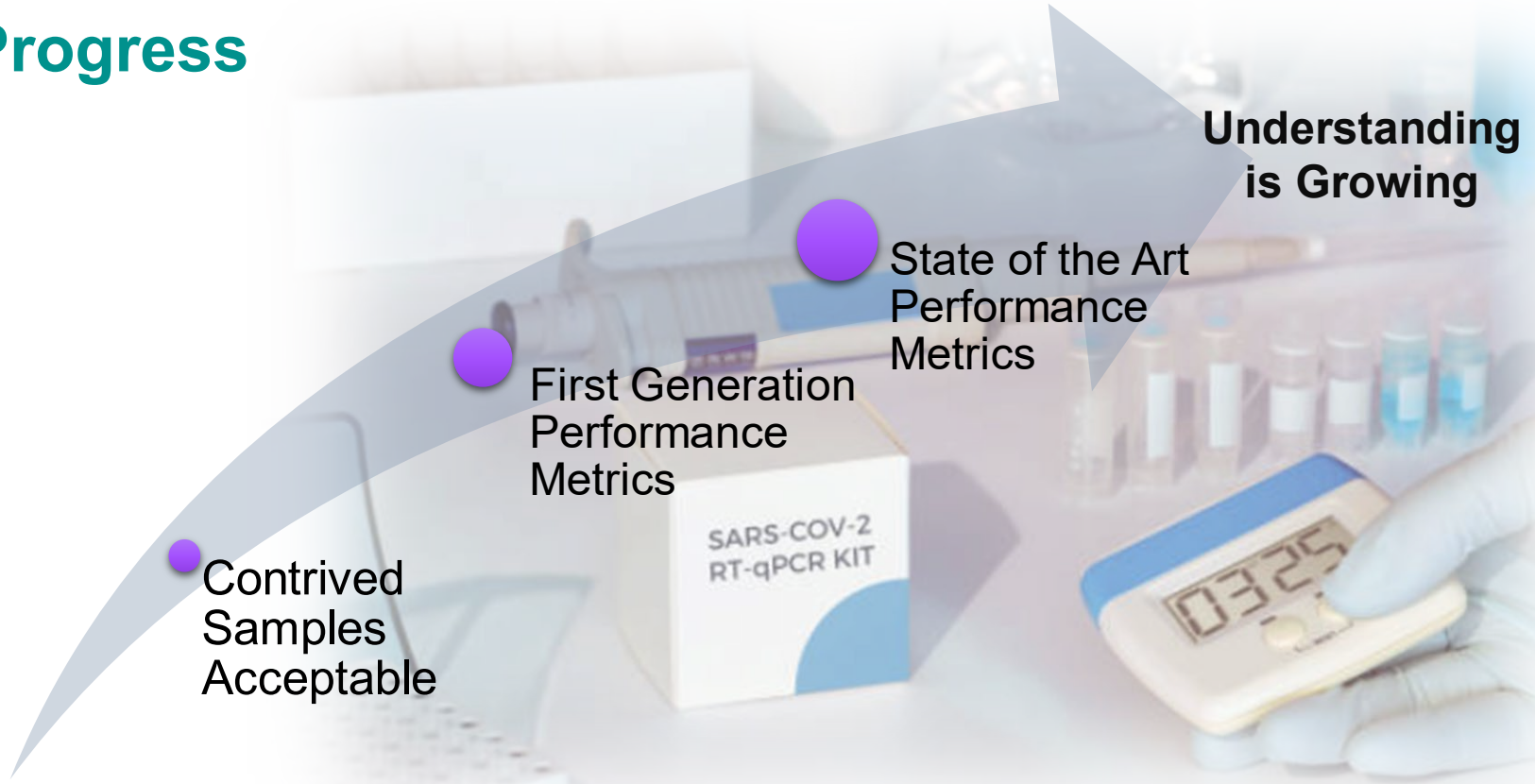
DRAFT GUIDANCE

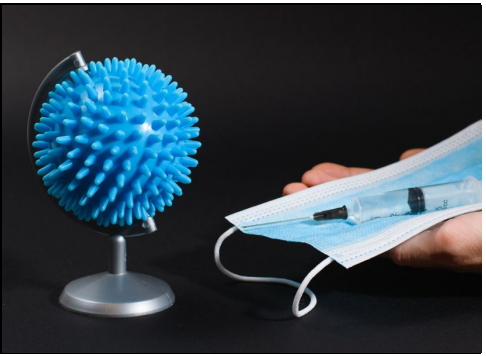
This draft guidance document is being distributed for comment purposes only.

Document issued December 2021.

https://www.fda.gov/media/155039/download

Progress





Legal Implications

POTENTIAL CLAIMS

- **Product Liability Claims (traditional claims)**
  - **Manufacturing defect**
  - **Design defect**
  - **Failure to warn**
  - **Negligence**
  - **Breach of implied warranty of fitness for a particular purpose**
  - **Breach of implied warranty of merchantability**
  - **Breach of express warranty**

POTENTIAL CLAIMS (CONT'D)

- Fraud and Consumer Protection Claims (new focus)
  - California Unfair Competition Act (Cal. Bus. & Prof. Code § 17200, et seq.)
  - California False Advertising Act (Cal. Bus. & Prof. Code § 17500, et seq.)
  - California Consumer Legal Remedies Act (Cal. Civ. Code § 1750)
  - Sherman Food, Drug and Cosmetic Law (Cal. Health & Safety Code § 109875)
  - Common law fraud
- Breach of Contract Claims
  - Breach of implied warranty
  - Breach of express warranty
  - Promissory estoppel

TYPES OF CASES

- Individuals vs. companies;
- Companies vs. companies;
- States vs. companies
- Mass tort suit
- Class action

COMMON ALLEGATIONS

- Marketed without EUA or De Novo 510(k)
  - Tests marketed before May 2020
  - Fraudulent tests
- Untrue or misleading representations (on product package; on company website; on owner's personal social media)
  - FDA approved – check the FDA website
  - FDA registered – Misleading
  - Personal testimonials – Misleading
  - Treatment for COVID – False
  - Prevent infection – False

COMMON ALLEGATIONS (CONT'D)

- Laboratory non-compliance and deficiencies
  - Laboratories testing for COVID must meet all requirements mandated in California and federal CLIA (Clinical Laboratory Improvement Amendments) law
- Testing not effective (product liability claims)
  - False positive
    - Emotional distress, social stigma
  - False negative
    - Physical injuries, injuries to others

Washington State
Office of the Attorney General

Attorney General
Bob Ferguson

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Home | News | News Releases | AG Ferguson: Center for COVID Control blocked from operating testing centers in Washington while case continues

AG Ferguson: Center for COVID Control blocked from operating testing centers in Washington while case continues

FOR IMMEDIATE RELEASE:
Feb 17 2022

The company also agreed to permanently stop all oper

OLYMPIA — Attorney General Bob Ferguson today anr
Illinois-based testing company Center for COVID Contr
testing services or collect consumer health informatio

In addition, as part of the court order, the company ag
Washington-based testing centers on or about Jan. 13,

The case will now enter the discovery phase, and will

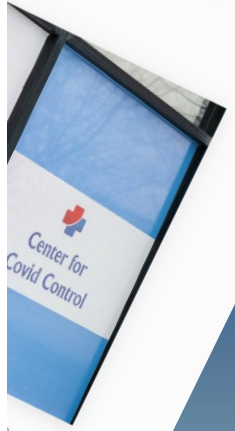
"Calling this conduct a 'scam' is an understatement," F
thousands of Washingtonians. Our investigation put a

CITYWIDE

Center For COVID Control Gets Sued By Another State, Which Alleges Local Owners Funneled Millions To Themselves While Doing Faulty Testing

The locally based company has
attorneys general and is
general filed suit
business" ag

been sued by three states'
gated by the FBI. Oregon's attorney
companies should "never do



4, 2022

Check The FDA Database Before Purchasing The Tests

Q: What in vitro diagnostic tests for COVID-19 have been issued an Emergency Use Authorization or marketing authorization? (9/27/22)

A: All in vitro diagnostic tests that have been issued an Emergency Use Authorization (EUA) are listed on the COVID-19 In Vitro Diagnostics EUAs page.

Tables of in vitro diagnostic test EUAs can be found for each type of COVID-19 test:

- Molecular Diagnostic Tests for SARS-CoV-2
- Antigen Diagnostic Tests for SARS-CoV-2
- Other Tests for SARS-CoV-2
- Serology and Other Adaptive Immune Response Tests for SARS-CoV-2
- IVDs for Management of COVID-19 Patients

On March 17, 2021, the FDA granted the first marketing authorization using the De Novo review pathway for the BioFire Respiratory Panel 2.1 (RP2.1). On November 1, 2021, the FDA cleared the first 510(k) for the BioFire COVID-19 Test 2.

Fraudulent Coronavirus Disease 2019 (COVID-19) Products

Share | Tweet | Linkedin | Email | Print

The U.S. Food and Drug Administration is issuing **warning letters** to firms for selling fraudulent products with claims to prevent, treat, mitigate, diagnose or cure coronavirus disease 2019 (COVID-19). We are actively monitoring for any firms marketing products with fraudulent COVID-19 prevention and treatment claims. The FDA is exercising its authority to protect consumers from firms selling unapproved products and making false or misleading claims, including, by pursuing warning letters, seizures, injunctions or criminal prosecutions against products and firms or individuals that violate the law.

Reporting Unlawful Sales of Medical Products on the Internet

Report a website that you think is illegally selling human drugs, animal drugs, medical devices, biological products, foods, dietary supplements or cosmetics.

How to Protect Yourself and Your Family From Coronavirus Fraud

The FDA advises consumers to be cautious of websites and stores selling products that claim to prevent, treat, or cure COVID-19.

Here are some tips to identify false or misleading claims.

- Be suspicious of products that claim to treat a wide range of diseases.
- Personal testimonials are no substitute for scientific evidence.
- Few diseases or conditions can be treated quickly, so be suspicious of any therapy claimed as a “quick fix.”
- If it seems too good to be true, it probably is.
- “Miracle cures,” which claim scientific breakthroughs or contain secret ingredients, are likely a hoax.

https://www.cdph.ca.gov/Programs/OSPHLD/LFS/Pages/COVID-19FAQ.aspx

Which labs can test for COVID-19?

Laboratories testing for COVID-19 must meet all requirements mandated in California and federal CLIA law.

Laboratories performing waived tests must have a CLIA certificate of waiver and a California clinical laboratory registration and a laboratory director and waived laboratory supervisor who meet all State and federal personnel requirements.

Laboratories performing tests classified under CLIA as moderate or high complexity must have a CLIA certificate of compliance or a certificate of accreditation and a California laboratory clinical license, as well as a laboratory director, general supervisor, technical supervisor, or technical consultant who meet all State and federal personnel requirements.

Please note that all laboratory-developed tests and all tests not classified by the FDA default to high-complexity testing, and require a CLIA certificate of compliance or certificate of accreditation and a California laboratory clinical license.

The FDA has not specified a specialty or subspecialty for SARS-CoV-2 testing. A laboratory with a license in any specialty or subspecialty may perform SARS-CoV-2 testing.

However, California law specifies the scope of practice for personnel licenses, and requires a laboratory director to hold a license that authorizes the licensee to direct testing in the specialty or subspecialty of a test as specified in BPC section 1207 and 17 CCR sections 1030.6, 1030.7, and 1031. Testing for COVID-19, the disease caused by the SARS-Cov-2 virus, is under the sub-specialty of virology in the specialty of microbiology. The specialist licenses that allow a person to direct molecular SARS-CoV-2 testing are clinical chemistry and clinical microbiology.

Therefore, a laboratory performing testing for COVID-19 must have a director licensed to direct one of these specialties, or the laboratory must have a clinical consultant, general supervisor, or technical supervisor qualified in these specialties, depending on the complexity of testing.

California law allows for multiple laboratory directors, with one who meets CLIA qualifications designated as the CLIA director; this gives a laboratory the option of adding a person qualified to direct COVID-19 testing as a co-director.

California licensed personnel authorized to direct moderate and high complexity COVID-19 testing include the following:

- Board Certified Pathologist
- Doctor of Medicine or Doctor of Osteopathy with experience directing a non-waived CLIA certified laboratory.
- Clinical Laboratory Bioanalyst
- Clinical Chemist
- Clinical Microbiologist

PREP DEFENSE – The PREP Act

Immunity under Public Readiness and Emergency Preparedness Act of 2005 (the "PREP Act") (42 U.S.C. § § 247d-6d, 247d-6e):

In general. Subject to the other provisions of this section, a covered person shall be immune from suit and liability under Federal and State law with respect to all claims for loss caused by, arising out of, relating to, or resulting from the administration to or the use by an individual of a covered countermeasure if a declaration under subsection (b) has been issued with respect to such countermeasure.

PREP DEFENSE – The PREP Act (Cont'd)

- Persons covered: manufacturers, distributors, program planners, qualified persons who prescribe, administer, or dispense countermeasures;
- Activities covered: development, manufacture, testing, distribution, administration, and use of countermeasures;
- Countermeasures covered: vaccines, drugs, medical devices (including diagnostic tests)
- Claims covered: tort liability except for willful misconduct.

PREP DEFENSE – Willful Misconduct

(c) Definition of willful misconduct

(1) Definition

(A) In general. Except as the meaning of such term is further restricted pursuant to paragraph (2), the term "willful misconduct" shall, for purposes of subsection (d), denote an act or omission that is taken—

- **(i) intentionally to achieve a wrongful purpose;**
- **(ii) knowingly without legal or factual justification; and**
- **(iii) in disregard of a known or obvious risk that is so great as to make it highly probable that the harm will outweigh the benefit.**

42 U.S.C.S. § 247d-6d (c)(1)

PREP DEFENSE – Willful Misconduct (Cont'd)

- **Definition of "willful misconduct," 42 USC § 247d-6d(c-d):**
  - Initiation of an enforcement action by the federal government that resulted in a "covered remedy;" Id. at (c)(5);
- **Definition of an "enforcement action:" Id. at (c)(5)(B)(i)**
  - Injunction,
  - Mandatory recall,
  - A revocation based on willful misconduct, of an authorization under section 564 of such Act.
- **Definition of "covered remedy:"**
  - A revocation of an authority under section 564. Id. at (c)(5)(B)(i)(I).

PREP DEFENSE – Summary

- Covered:
  - FDA approved/De Novo 510(k) cleared;
  - EUA issued;
  - No willful misconduct (no fraud claims against you)
- Not covered:
  - No FDA approval/authorization/clearance
  - Willful misconduct
    - Fraud
    - Injunction
    - Mandatory recall
    - Revocation of EUA based on willful misconduct
  - State contract law claims

STATE LAW DEFENSE

- State law product liability defense
  - Manufacture met industrial standards;
  - Expert opinion on design and warning defects;
  - Defenses against negligence;
  - No causation
  - No injuries/damages
- State law breach of contract defense
- State law fraud defense

EXISTING CASES

- **People v. Applied Biosciences Corp., 2021 Cal. Super. LEXIS 6787 (Superior Court of California, County of Los Angeles);**
  - Allegations: Defendants' "At-Home COVID-19 Test Kit" violated California's Unfair Competition Act (Bus. & Prof. Code § 17200 et seq.), California False Advertising Act (Bus. & Prof. Code § 17500 et seq.), California Health and Safety Code section 109875 et seq.
  - The parties submitted a Joint Stipulation for Final Judgment and Permanent Injunction:
    - Defendants immediately and permanently enjoined from continuing violation;
    - Monetary relief:
      - $50,000 under Cal. Bus. & Prof. § § 17206, 17503;
      - $15,000 paid to Los Angeles County Treasurer and Tax Collector
      - $35,000 civil penalties
      - Direct refund to all consumers who purchased the kits from Defendants

EXISTING CASES (CONT'D)

- **People v. Yikon Genomics, 2020 Cal. Super. LEXIS 3615**
  - Allegations: Defendants' "At-Home COVID-19 Test Kit" violated California's Unfair Competition Act (Bus. & Prof. Code § 17200 et seq.), California False Advertising Act (Bus. & Prof. Code § 17500 et seq.), California Health and Safety Code section 109875 et seq.
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      - $35,000 civil penalties
      - Direct refund to all consumers who purchased the kits from Defendants

EXISTING CASES (CONT'D)

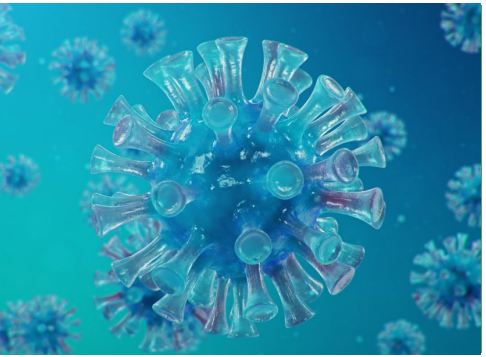
- **United States SEC v. Wellness Matrix Grp., Inc., No. 8:21-cv-01031-SSS-DFM, 2022 U.S. Dist. LEXIS 193715 (C.D. Cal. Oct. 21, 2022)**
  - COVID test developer defrauded investors in misrepresenting the FDA approved or registered its COVID testing kits;
  - Owner promoted test kits on his personal Twitter account, falsely claiming that Wellness Matrix was selling "FDA approved" "home test kits" to "stop Corona Before It Starts."
  - SEC's motion for summary judgment granted.

EXISTING CASES (CONT'D)

- **Workcare, Inc. v. Plymouth Med., LLC, No. 8:21-cv-00864-DOC-ADS, 2021 U.S. Dist. LEXIS 168341 (C.D. Cal. Aug. 20, 2021)**
  - Entered into a contract to provide COVID home test kits when the EUA was pending;
    - The FDA Policy expressly authorized serology tests to be manufactured, distributed and used in the United States 'for a reasonable period of time' while the manufacturer was performing its request for an EUA, so long as the tests were validated and the manufacturer notified FDA
  - **EUA application was denied;**
  - **Plaintiff filed suit asserting breach of contract claims:**
    - Breach of implied warranty
    - Breach of express warranty
    - Promissory estoppel

EXISTING CASES (CONT'D)

- **Workcare, Inc. v. Plymouth Med., LLC, No. 8:21-cv-00864-DOC-ADS, 2021 U.S. Dist. LEXIS 168341 (C.D. Cal. Aug. 20, 2021)**
  - PREP Act does not apply
  - Breach of express warranty – dismissed
    - The Tests are provided by Company to Purchaser pursuant to the Policy for Diagnostic Tests for Coronavirus Disease-2019 during the Public Health Emergency issued on the web on May 4th, 2020 [] by the U.S. Department of Health and Human Services along with the Food and Drug Administration
  - Breach of implied warranty of merchantability – dismissed
    - The tests had not been denied an EUA at the time of use, so no breach of the implied warranty is sufficiently alleged.
  - Promissory estoppel
    - Failed to keep the promise of replacing unusable tests given the FDA's unexpected denial of EUA



Key Takeaways

Key Takeaways

- Interpretation of COVID-19 data requires a careful scientific assessment of key parameters, including testing methods and sampling protocols.

- Regulations regarding COVID-19 tests have historically evolved to match the phase of the pandemic.

Key Takeaways – Legal

- Ensure PREP Act Protection:
  - Obtain applicable regulatory approval for the test and the laboratory;
  - Monitor the test's regulatory status on FDA website;
  - Check the FDA's database before purchasing tests;
  - No misleading representations anywhere;
  - Initiate voluntary recall if necessary;
  - Any other actions necessary.

Questions

Presenters

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