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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD Presents:

COVID-19 & the Liver: SARS-CoV-2 Diagnostic Testing and Vaccine Development

July 9, 2010
5:00pm – 6:00pm EDT

Presenters:
Joel Ernst, MD
Gopi Patel, MD

Moderator:
Mark W. Russo, MD, MPH, FAASLD

COVID-19 and the Liver: SARS-CoV-2 Diagnostic Testing and Vaccine Development

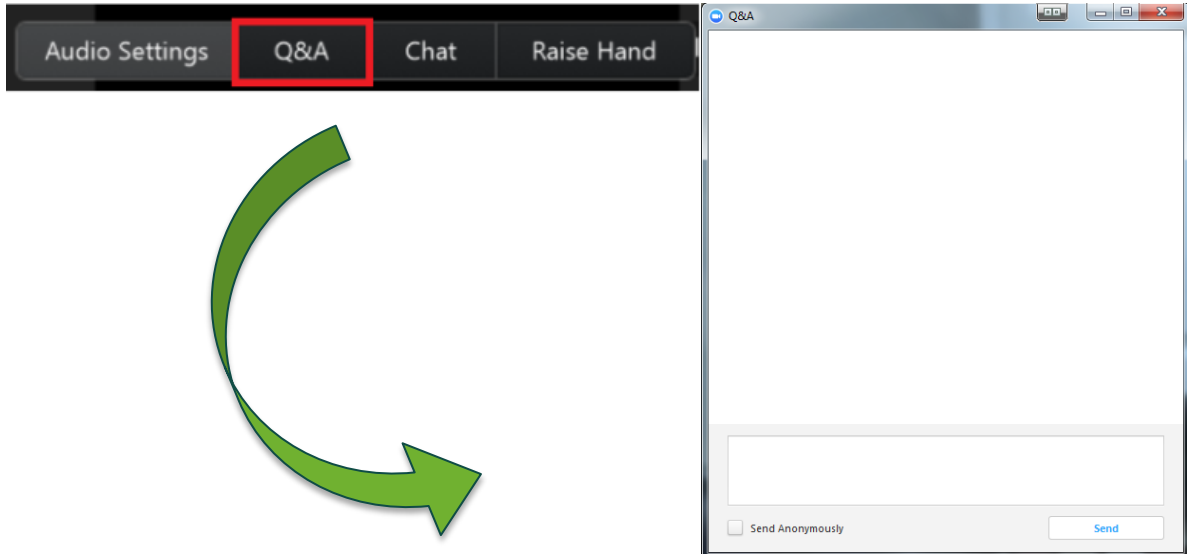
Mark W Russo, MD MPH FAASLD
Carolinas Medical Center-Atrium Health

Webinar Agenda

- Housekeeping Items – Dr. Mark Russo
- Webinar Contributors – Dr. Mark Russo
- Presenter Introductions – Dr. Mark Russo
- SARS-CoV-2 Diagnostic Testing & Vaccine Development – Dr. Mark Russo
- Diagnostics and COVID-19 – Dr. Gopi Patel
- COVID-19 Vaccines – Dr. Joel Ernst
- Panel Discussion / Q&A

Webinar Q&A

Submit your questions in the Q&A box at the top or bottom of your screen.



Questions will be answered at the end of the presentation.

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- Co-chair, Elizabeth C. Verna, MD, MS, Columbia University (New York)
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- Andrew Reynolds, (Patient Advocate)
- Raymond Chung and K. Rajender Reddy (ex-officio)

Webinar Moderator

Mark W. Russo, MD, MPH, FAASLD

Medical Director of Liver Transplantation, Chief, Division of Hepatology, and Clinical Professor of Medicine

Carolinas Medical Center - Atrium Health

Webinar Presenter

Gopi Patel, MD MS

Hospital Epidemiologist – The Mount Sinai Hospital

Associate Professor, Infectious Diseases – Icahn School of Medicine at Mount Sinai

Webinar Presenter

Joel Ernst, MD

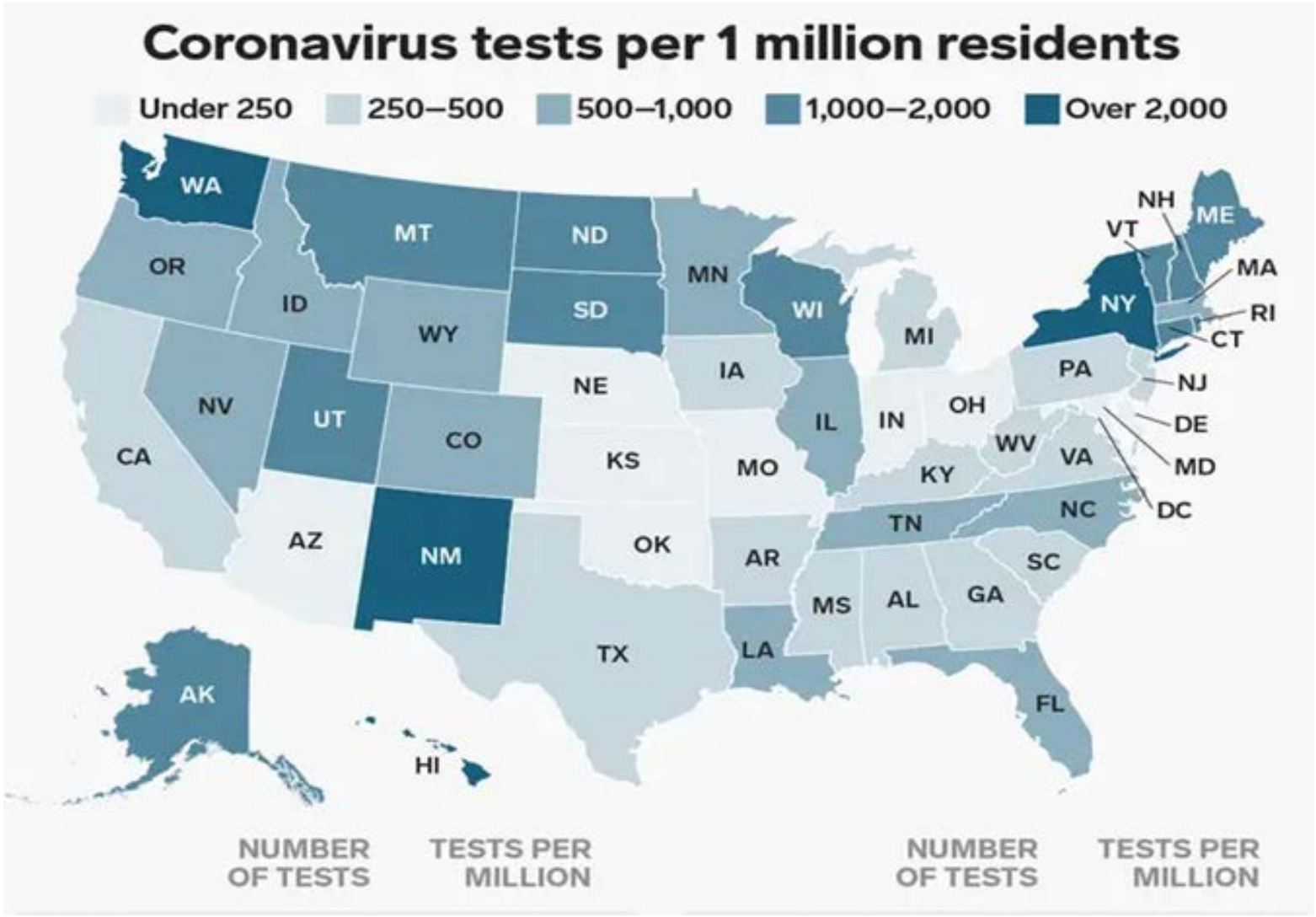
Professor of Medicine and Chief of the Division of Experimental Medicine

University of California San Francisco

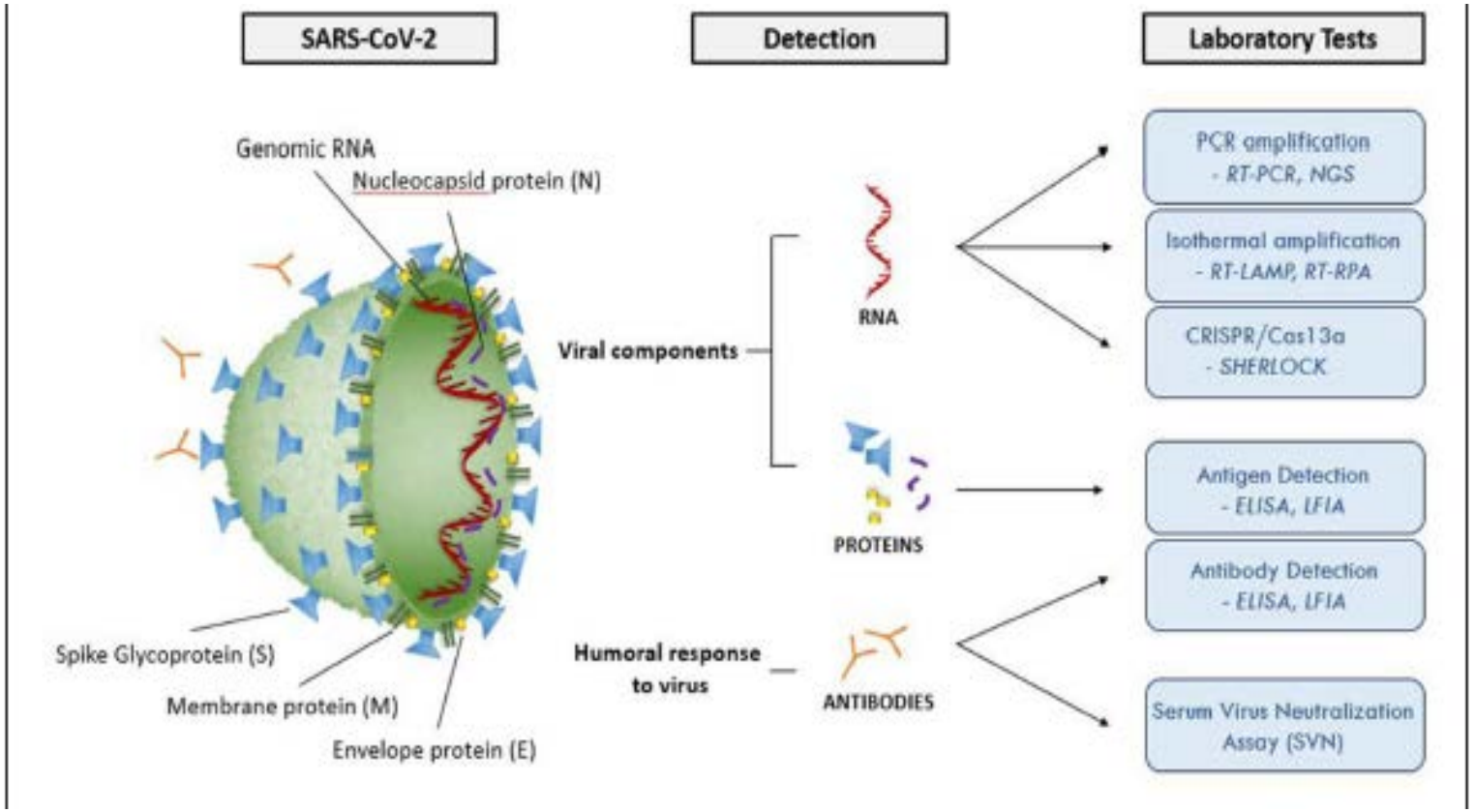
Webinar Panelist

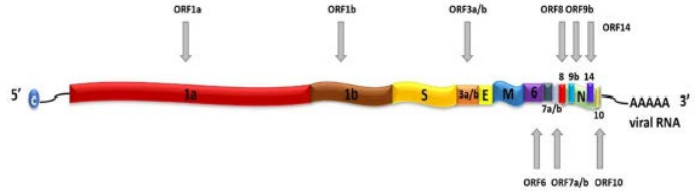
- **Peter Chin-Hong, MD**, University of California, San Francisco
- **Mercedes Martinez, MD**, New York-Presbyterian
- **Philippe J. Zamor, MD, FAASLD**, Carolinas Medical Center

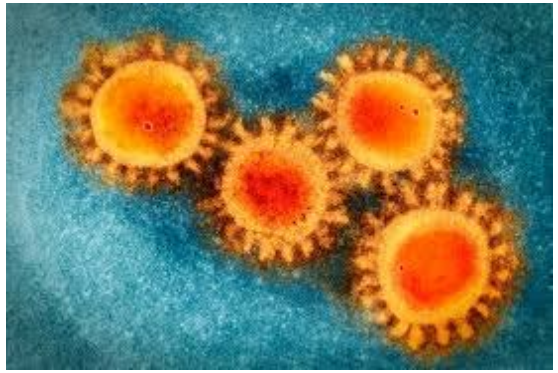
COVID-19 Testing



U.S
Cases >3 million
Deaths 131,000

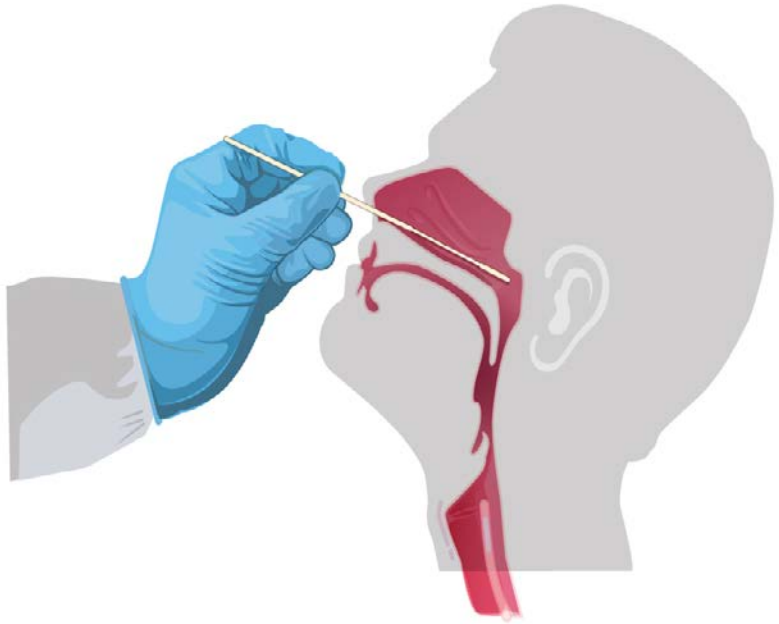






D'Cruz Rj, et al. Frontiers in Cell and Develop Biol 2020;8:1-8

Testing for SARS-CoV-2



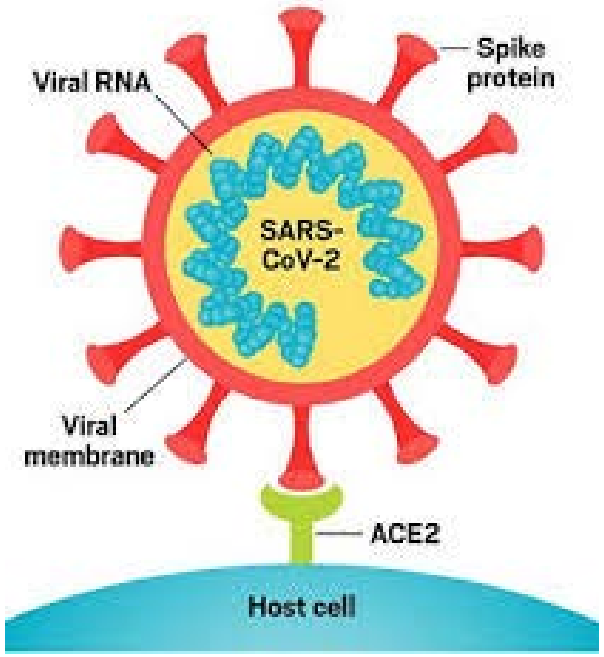
<u>Nasal mid-turbinate (NMT) swab, also called Deep Nasal Swab</u>
Insert swab less than one inch (about 2 cm) into nostril (until resistance is met at turbinates). Rotate the swab several times against nasal wall and repeat in other nostril with the same swab.

<u>Anterior nares specimen</u>
Insert the swab at least 1 cm (0.5 inch) inside the nostril (naris) rotating the swab and leaving in place for 10 to 15 seconds. Sample both nostrils with same swab.

<u>Nasopharyngeal wash/aspirate or nasal wash/aspirate</u>
Attach catheter to suction apparatus. Instill 1 mL-1.5 mL of non-bacteriostatic saline (pH 7.0) into one nostril. Begin gentle suction/aspiration and remove catheter while rotating it gently.

Saliva tests
Home Kit tests

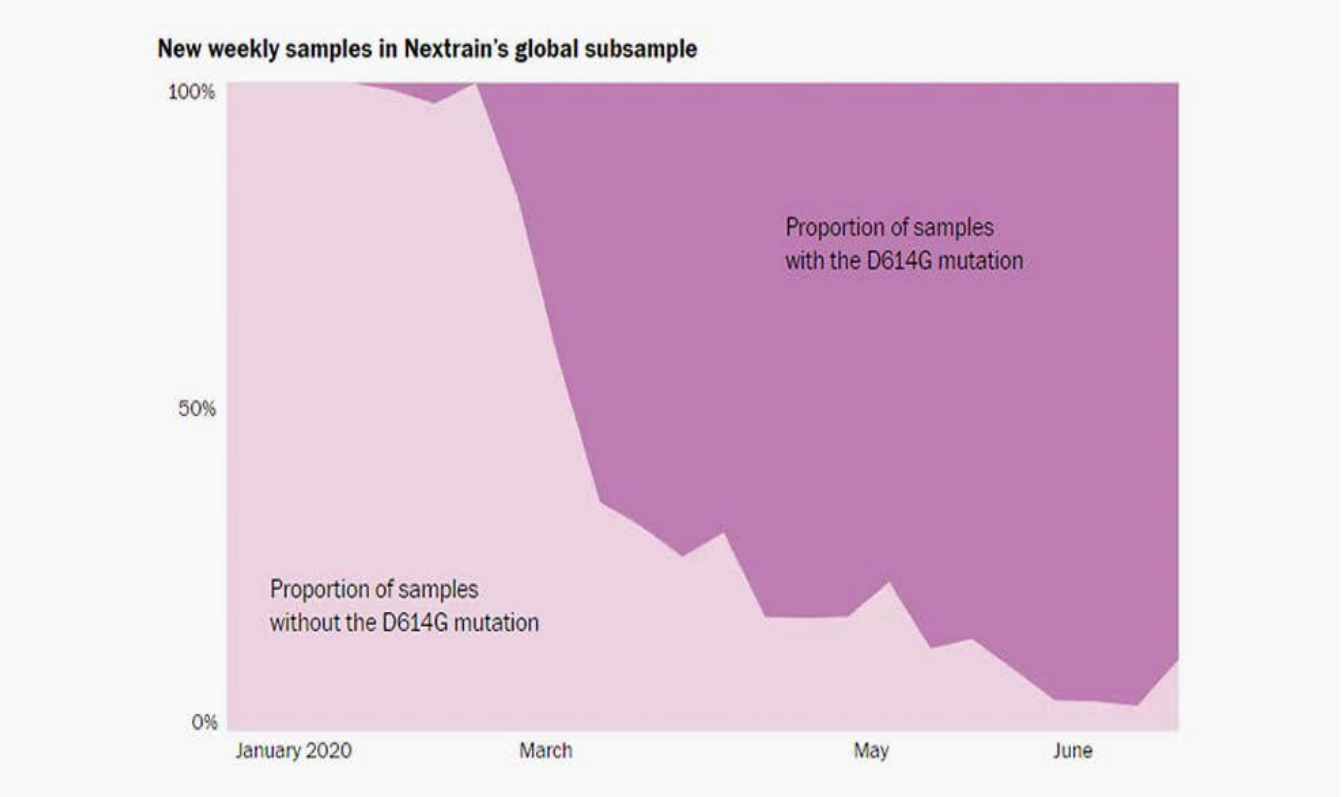
Testing for Antibody to SARS-CoV-2

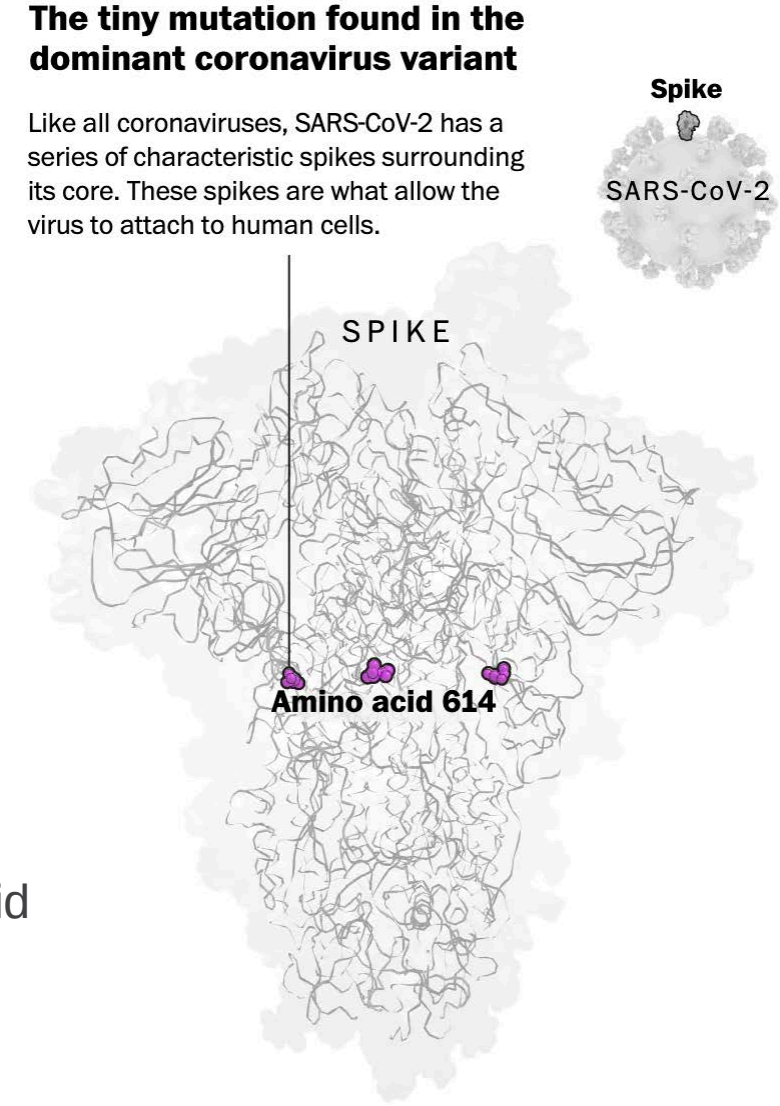


The two major antigenic targets of SARS-CoV-2 virus against which antibodies are detected are
-Spike glycoprotein (S) and nucleocapsid phosphoprotein (N).
-S protein is essential for virus entry and is present on the viral surface
-N protein is the most abundantly expressed immunodominant protein that interacts with RNA.

- Multiple forms of S protein — full-length (S1+S2) or partial (S1 domain or receptor binding domain [RBD])
- N is more conserved across coronaviruses than S, and within S, RBD is more conserved than S1 or full-length S.
- Antibodies that bind to the receptor binding domain of the spike protein that allows viral entry into the cell through ACE2 receptor is speculated to be most effective.

SARS-CoV-2 mutation



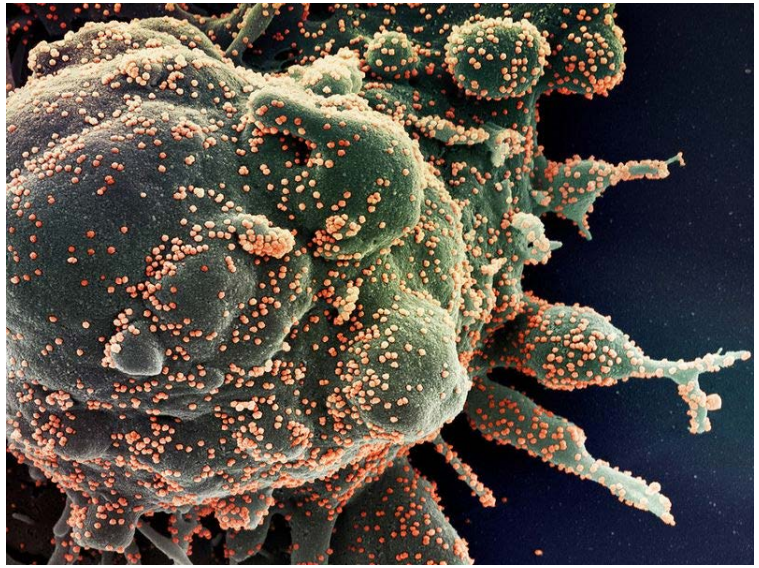


A mutation affecting the virus's spike protein changed amino acid 614 from “D” (aspartic acid) to “G” (glycine). D614G mutation

Washington Post June 29,2020, Aaron Steckelberg

Vaccine development
>100 vaccine projects
At least 8 vaccines in trials
mRNA
DNA vaccine to MERS
ChAdOx1 nCoV-19 vaccine or a licensed vaccine (MenACWY)
molecular clamp technology designed to lock the ‘spike’ protein into a shape

ChAdOx1 nCoV-19 is made from a virus (ChAdOx1), which is a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees, that has been genetically changed so that it is impossible for it to replicate in humans.

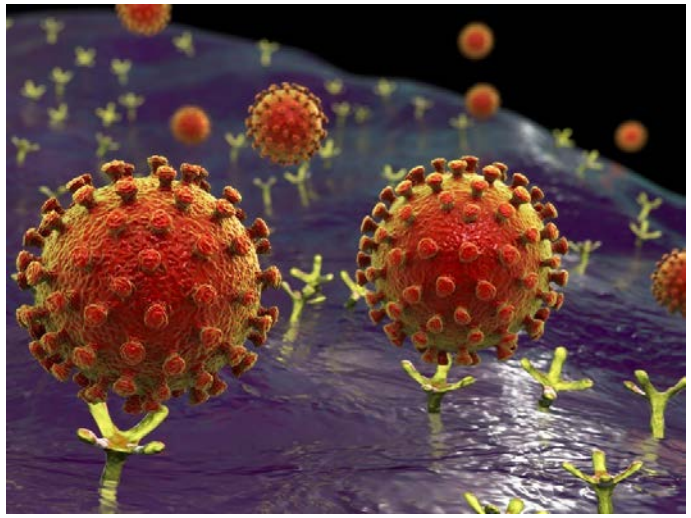


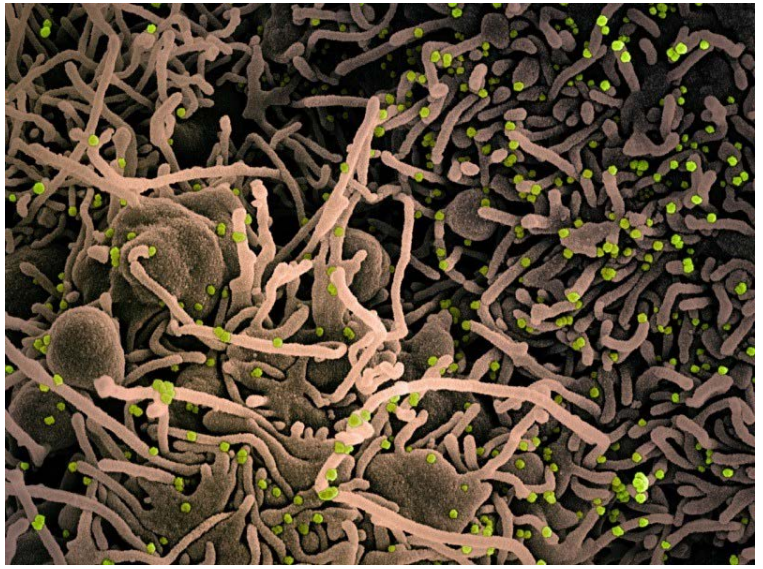
http://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials

GUIDANCE DOCUMENT

Development and Licensure of Vaccines to Prevent COVID-19
Guidance for Industry
JUNE 2020

https://www.fda.gov/media/139638/download





Diagnostics and COVID-19

Gopi Patel, MD MS
Hospital Epidemiologist, The Mount Sinai Hospital
Associate Professor, Infectious Diseases
Icahn School of Medicine at Mount Sinai

- No conflicts of interest

- **Test! Test! Test!**
  - Early response to the pandemic hampered by inability to rapidly and accurately diagnose SARS-CoV-2 infection
  - First CDC issued tests had issues with negative controls
  - FDA Emergency Use Authorization (EUA)

- **Real-time reverse transcriptase polymerase chain reaction (rRT-PCR)**
  - Genetic sequence published January 10, 2020
  - Platforms repeats amplification process (40 cycles) until cDNA can be detected
  - **“Gold-standard”** for diagnosis of acute infection with SARS-CoV-2
- **EUA process led to rapid approval of multiple testing platforms**
  - Abbreviated format in the setting of a public health emergency
  - Permitted the use of “contrived” specimens
    - Use of either known positive or contrived specimens can lead to overestimation of sensitivity since in practice infectious material can be missed

/www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/ published 6May20; accessed 5Jul20

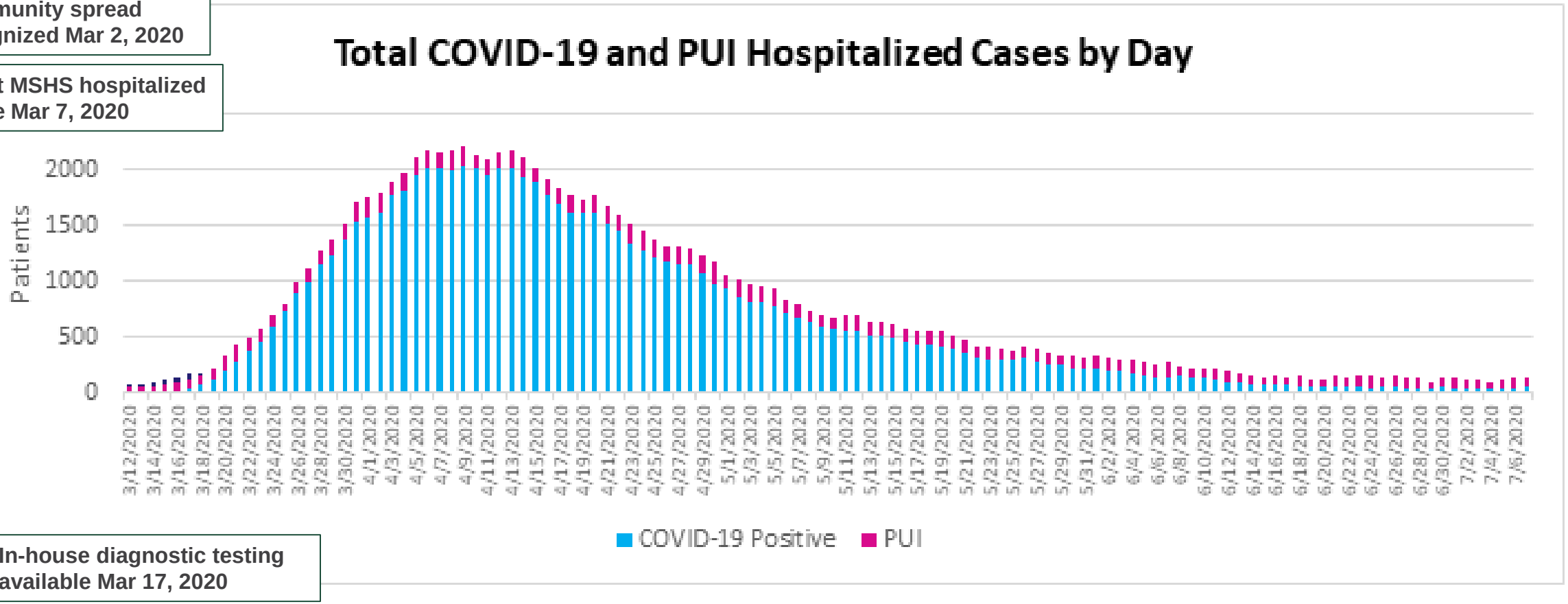
- **Supply chain instability with increased demand for viral transport media, swabs, and reagents**
  - Personal protective equipment (PPE) required for testing
  - Protecting healthcare workers from unnecessary exposures
- **Limited testing and overwhelmed healthcare systems**
  - Prioritized testing for those requiring hospitalization
  - Inability to rapidly and accurately identify pre-symptomatic and asymptomatic cases leading to “silent-transmission”

Mount Sinai

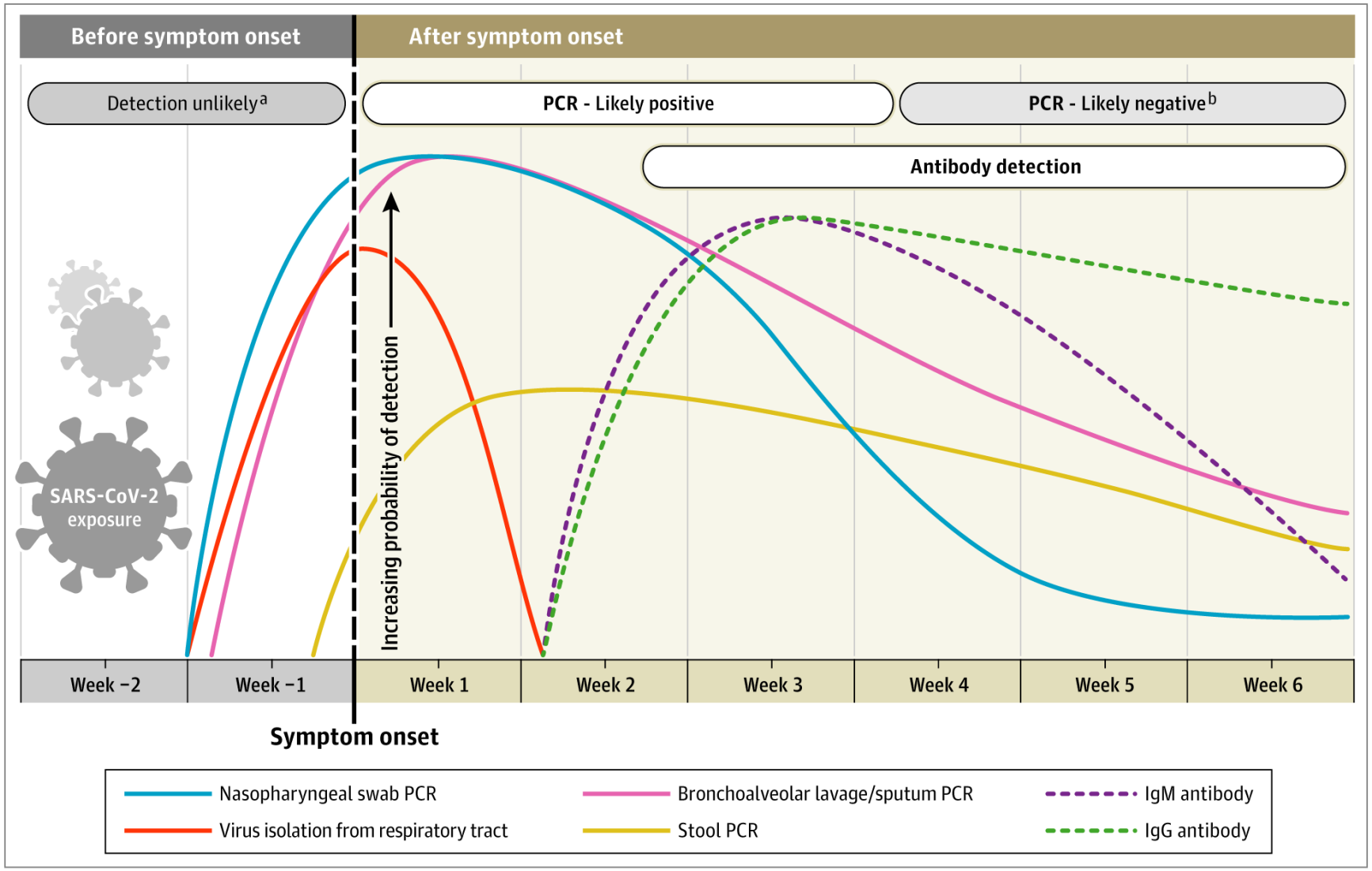
First case diagnosed in NYS Feb 29, 2020

Community spread recognized Mar 2, 2020

First MSHS hospitalized case Mar 7, 2020



In-house diagnostic testing available Mar 17, 2020



Sethuraman N *et al. JAMA.* 2020. 323(22) 2249-51
Wolfel R *et al. Nature.* 2020 May;581(7809):465-469
Bullard J *et al. Clin Infect Dis.* 2020 May 22;ciaa638. doi: 10.1093/cid/ciaa638.

- **False-negatives**
  - May not be appropriately isolated
  - Prevents enrollment in clinical trials
- **Role of repeat testing**
  - Early infection can be missed
    - PCR positivity may decline more slowly in sputum and lower respiratory tract specimens
  - Clinical syndrome consistent with COVID-19
    - Alternative site (e.g., lower respiratory tract specimen)

https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/ published 6May20; accessed 5Jul20
Woloshin S *et al. New Engl J Med.* June 5, 2020. DOI: 10.1056/NEJMp2015897

- **Pretest-probability influences how we interpret tests**
  - Dependent on prevalence, exposure history, and symptoms
  - If pre-test probability high the test loses its value
- **“Real-world” PCR sensitivity is considered to be ~70%**
  - Even lower with antigen testing
- **Efforts to decrease pre-test probability matter**
  - Masking, social distancing, and PPE

- **Antigen testing**
  - As of July 9, two tests with EUA from the FDA
  - Quick and inexpensive (point-of-care)
  - Detect protein fragments
  - Specific and not sensitive for SARS-CoV-2 (risk of false-negative)

- **Defining the role of asymptomatic testing**
  - Consider when there is **adequate testing capacity**
  - High prevalence (10% or greater in the community)
  - Major surgery planned or when aerosol-generating procedures anticipated
  - Immunocompromised hosts
  - Known contacts of a laboratory-confirmed case
  - Congregate settings

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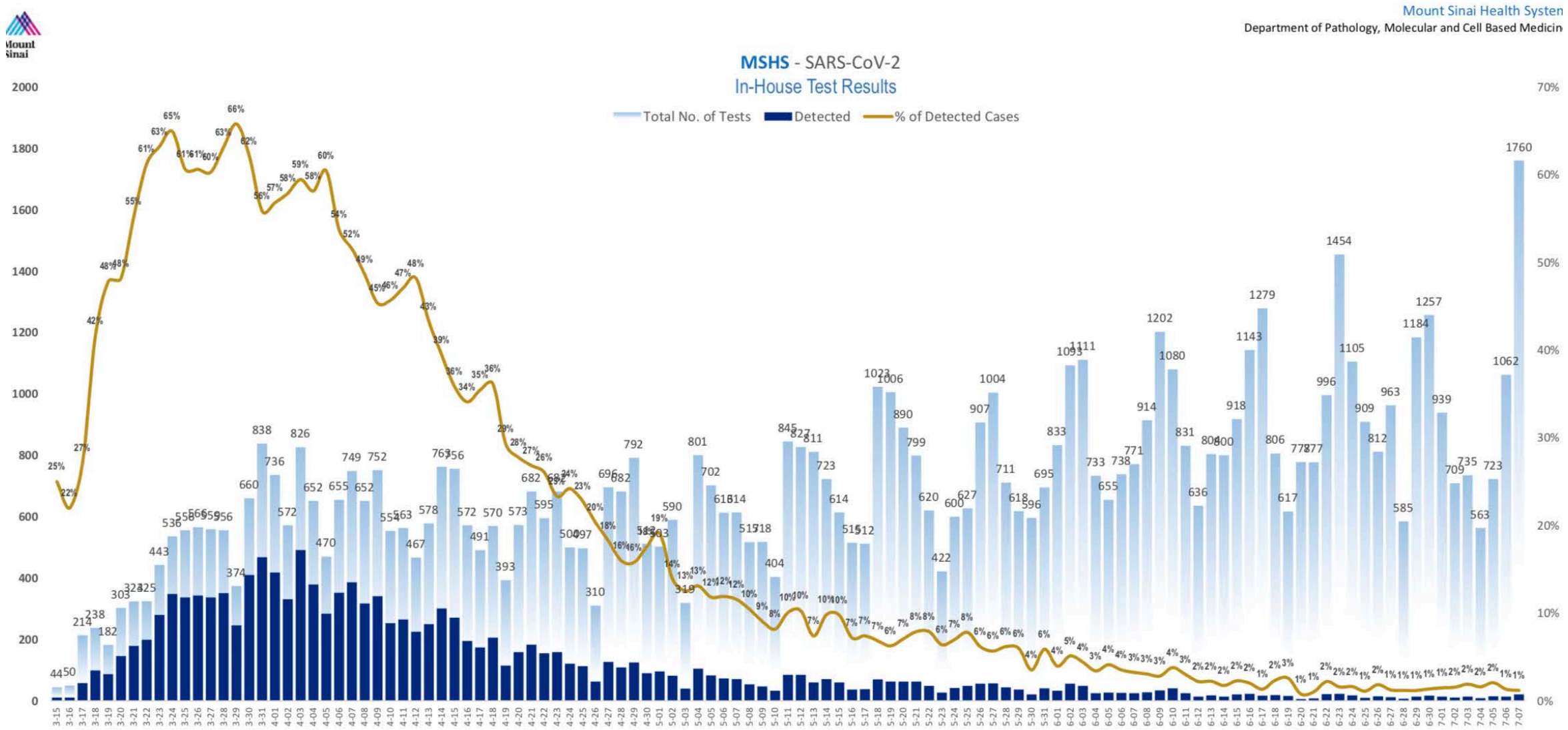

Mount Sinai Health Systen
Department of Pathology, Molecular and Cell Based Medicin
MSHS - SARS-CoV-2
In-House Test Results
Total No. of Tests
Detected
% of Detected Cases

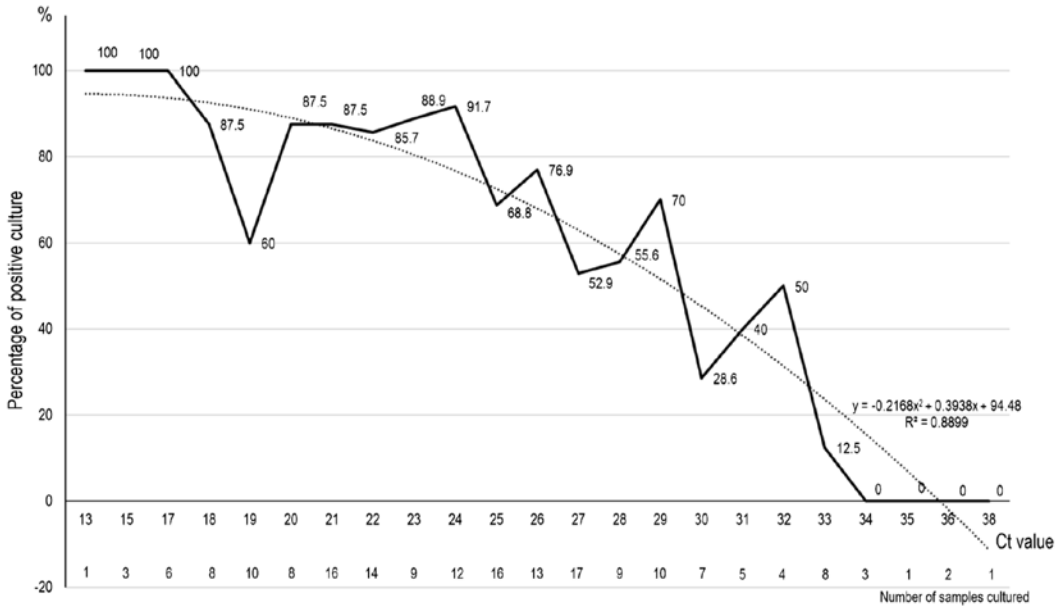
- **Persistent or intermittent PCR positivity and discontinuation of transmission-based precautions**
  - **Symptom-based strategy***
    - Studies demonstrate inability to isolate replicating virus ≥ 9 days from symptom-onset in immune competent hosts
  - **Test-based strategy**
    - More conservative but resource intensive
    - Recommended for vulnerable individuals at high risk for morbidity
    - Immunocompromised may have prolonged shedding

*** Time-based strategy** can be used for asymptomatic patients based on time of diagnosis

https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html updated 2May20; accessed 5Jul20
https://www.cdc.gov/coronavirus/2019-ncov/community/strategy-discontinue-isolation.html updated 3May20; accessed 5Jul20

o Cycle thresholds (Ct)

- Lower Ct in hospitalized
- Evidence that replication-competent virus is not isolated in culture at higher Ct
  - No correlation with illness length and duration of PCR positivity
- Illness severity may correlate with prolonged viral shedding



Wolfel R *et al. Nature.* 2020 May;581(7809):465-469
Bullard J *et al. Clin Infect Dis.* 2020 May 22; doi: 10.1093/cid/ciaa638
Binnicker M. *Clin Infect Dis.* 2020 Jun 6; doi.org/10.1093/cid/ciaa735

La Scola B *et al. Eur J Clin Microbiol Infect Dis.* 2020; 39: 1059-61
van Kampen JJA *et al.* https://www.medrxiv.org/content/10.1101/2020.06.08.20125310v1 published online 9Jun20

o **Repeat positives and reinfection?**

- On average 45 days [3-82 days] from symptom onset
  - 37.5% had symptoms which prompted testing
- 709 contacts traced with 3 “new” cases
  - Unable to culture virus and with evidence of **neutralizing antibodies**
- Repeat isolation period and extensive contact investigations suspended

https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030 updated 3Jun20; accessed 5Jul20

- **Serological tests (antibody testing)**
  - Identify plasma donors
  - Confirm patients had SARS-CoV-2 infection
    - Can be used to support clinical assessment in persons presenting late in illness or with post-infectious syndromes (e.g., MIS-C)
  - Serosurveillance
  - Tool to determine immunologic response after vaccination
    - Establish correlation with immunity?

Amanat, F *et al. Nat Med* (2020). https://doi.org/10.1038/s41591-020-0913-5
Stadlbauer D *et al.* https://www.medrxiv.org/content/10.1101/2020.06.28.20142190v1 posted 29Jun20

- **Types of commercial assays**
  - Enzyme-linked immunosorbent assays (EIA/ELISA)
  - Lateral Flow Assays
- **Minimize the false positive rate (high specificity)**
  - Additional data required prior to altering public health recommendations
  - Mask, social distance, wear appropriate PPE

Adams ER *et al.* https://www.medrxiv.org/content/10.1101/2020.04.15.20066407v2 posted 7May20
Amanat F *et al. Immunity*. 2020; 52(4) 583-9
https://www.fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-test-performance accessed 8Jul20

- **Limitations in current <u>diagnostic</u> testing**
  - Measuring test sensitivity in asymptomatic individuals is a priority
  - **False negative results** not uncommon thus cannot reliably rule out infection if the pretest probability is high
- **Limitations in current <u>serologic</u> testing**
  - Risk of **false positive results** in low prevalence settings
    - Primarily qualitative
  - Unclear clinical utility and durability unknown

TO THE HEALTH CARE WORKERS FIGHTING FOR OUR LIVES, THANK YOU.

gopi.patel@mountsinai.org

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COVID-19 vaccines

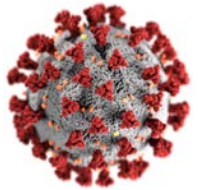
Joel Ernst, M.D.
Professor, Department of Medicine
Chief, Division of Experimental Medicine

UCSF
University of California
San Francisco
advancing health worldwide

o No conflicts of interest

Why are COVID-19 vaccines needed?

- Highly transmissable by the respiratory route, incapacitating and deadly



- Can be transmitted by asymptomatic/presymptomatic individuals
- Can become endemic; community (‘herd’) immunity is unlikely to be achieved by infection
- The economic and human impact of COVID-19 is large

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What do we know about immunity to COVID-19?

- Protective immunity may be transient after infection
- Neutralizing antibodies likely contribute to protection
- Presence of antibodies does not guarantee protection
  - Quantity and quality of antibodies not measured by routine assays
  - Some antibodies can be harmful ('Antibody-Dependent Enhancement'); the 'right' antibodies are needed

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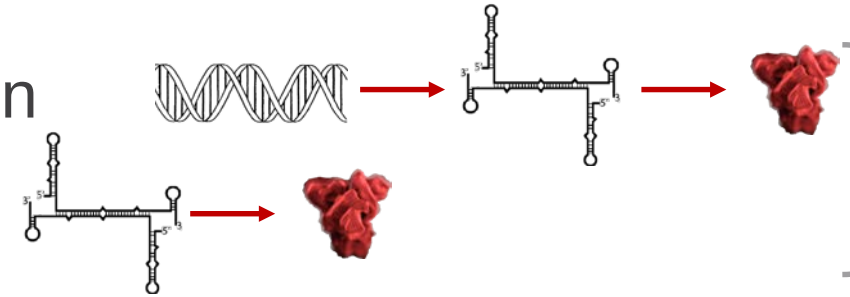
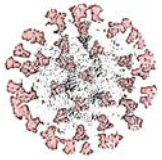
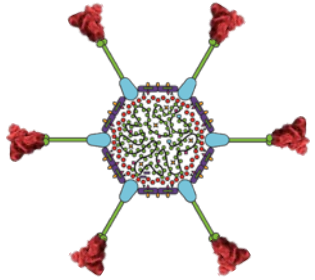
Multiple approaches to COVID-19 vaccines

- **Inactivated virus** (grow virus, chemically inactivate)  (Salk polio)
- **Attenuated virus** (modify virus for limited growth)  (Sabin polio)
- **Nucleic acid-based**:
  - DNA→RNA→protein antigen
  - RNA→protein antigen

 (Experimental)

- **Purified protein ± adjuvant**  (HBV, tetanus) **Virus-like particle**  (HPV)
- **Viral 'vector' delivery of antigen**  (Experimental)

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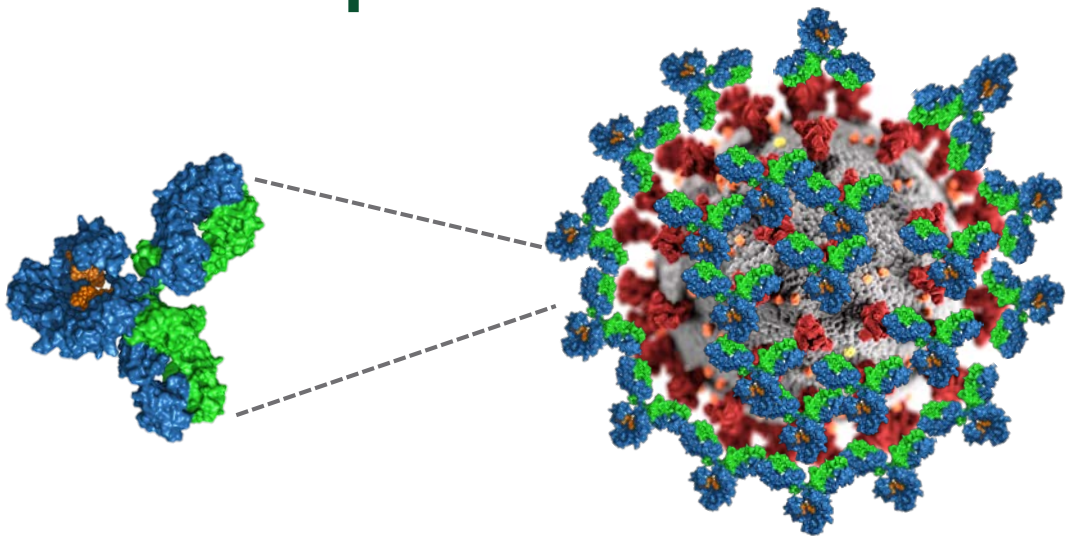
Goals of vaccine development



- Safety
- Generate neutralizing antibodies:
  - T cells may also contribute to protection
- Block infection where virus enters (mucosal immunity)
- Generate long-lived immunological memory
- Recognize viral targets that cannot mutate to escape

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COVID-19 vaccine development in progress

- o Nucleic acid (DNA or RNA) vaccines: ~20 groups
- o Viral vectored vaccines: ~25 groups
  - Multiple different viral vectors in use
- o Protein-based vaccines
  - Protein subunits: ~28 groups
  - Virus-like protein particles: 5 groups

What are the stages of vaccine development?

- [Discovery/development]
- **Is the vaccine safe?**
- Does the vaccine stimulate immune responses in humans?
- Does the vaccine protect humans from disease? (efficacy)
- Does the vaccine protect humans in the real world? (effectiveness)

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Other essential vaccine considerations

- Rapid large scale production essential in pandemic
- Must be economical on a global scale
- Must be stable, for populations regardless of location (avoid need for refrigeration)

Why does it take so long to develop a new vaccine?

Safety studies in humans require time, to observe for complications

Can ‘human challenge’ studies help?

- Vaccine protection can be determined in:
  - Large populations naturally exposed to infection (slow, expensive)
  - Small populations of volunteers experimentally exposed to infection (‘human challenge’) (more rapid, less expensive)
- Ethical concerns for human challenges when reliable curative treatment unavailable

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Thank you

Questions?

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Panel Discussion

Please submit your questions to the Q&A Chat now.