

Diagnosis and Monitoring of COVID-19 Infection

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Academia Nacional de Medicina de Colombia

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■ Overview of ARUP Laboratories

ARUP Laboratories

Born out of Academics in 1984

Invested in the Future of Lab Medicine



State of Utah (utah.gov)



University of Utah &
Hospitals (utah.edu)



(aruplab.com)
(arup.utah.edu)

- ARUP is an enterprise of the University of Utah & its Department of Pathology
- Nonprofit
- Full-service hospital lab & national reference lab
- 100+ pathologists and PhD laboratory medical directors
- Training & education facility for future pathologists & lab professionals (20+ pathology residents, 30+ clinical laboratory fellows)

Breadth of Testing & Support



Offers over **3,000** tests and test combinations



Operates **24/7/365**



Performs **99%** of all testing on-site (one location)
~70 thousand specimens daily



Access to support and expertise
Test interpretation support / Transfer of tests to clients who are ready to bring in house

4,000+
employees

25M+
specimens/year

~200
publications a year



Laboratory Divisions

60+ laboratories
provide full services

CHEMISTRY DIVISION

- Analytic Biochemistry
- Automated Core Laboratory
- Automated Endocrinology
- Calculi & Manual Chemistry
- Clinical Drugs of Abuse
- Clinical Toxicology
- Electrophoresis & Manual Endocrinology
- Mass Spectrometry
- Special Chemistry
- Trace & Toxic Elements

IMMUNOLOGY DIVISION

- Autoimmune Immunology
- Cellular & Innate Immunology
- Immunologic Flow Cytometry
- Immunology Core
- Microbial Immunology
- Protein Immunology
- Serologic Hepatitis-Retrovirus

INFECTIOUS DISEASE

- Bacteriology
- Infectious Disease Automated Testing
- Infectious Disease Antigen Detection
- Molecular Amplified Detection
- Molecular Hepatitis/Retrovirus
- Molecular Infectious Disease
- Mycology AFB
- Parasite & Fecal Testing
- Sequencing Infectious Disease
- Special Microbiology
- Virology

UNIVERSITY OF UTAH HEALTHCARE

- Hospitals and Clinics, Clinical Laboratories
(Stat labs at University hospital, Huntsman cancer hospital, community health clinics)

INTEGRATED ONCOLOGY AND GENETICS

- Biochemical Genetics
- Cytogenetics
- Fragment Analysis
- Genomics
- Immunogenetics
- Molecular Cytogenetics (microarray)
- Molecular Genetics
- Molecular Oncology
- Sequencing Genetics
- Special Genetics

PATHOLOGY

- Anatomic Pathology
- Cytology
- Hematologic Flow Cytometry
- Hemostasis/Thrombosis
- Histology
- Immunohistochemistry
- Special Hematology

SUPPORT SERVICES

- Automated Specimen Management
- Automation Engineering
- Clinical Trials
- PharmaDx
- Specimen Processing, and other specialized processing

TRANSFUSION MEDICINE

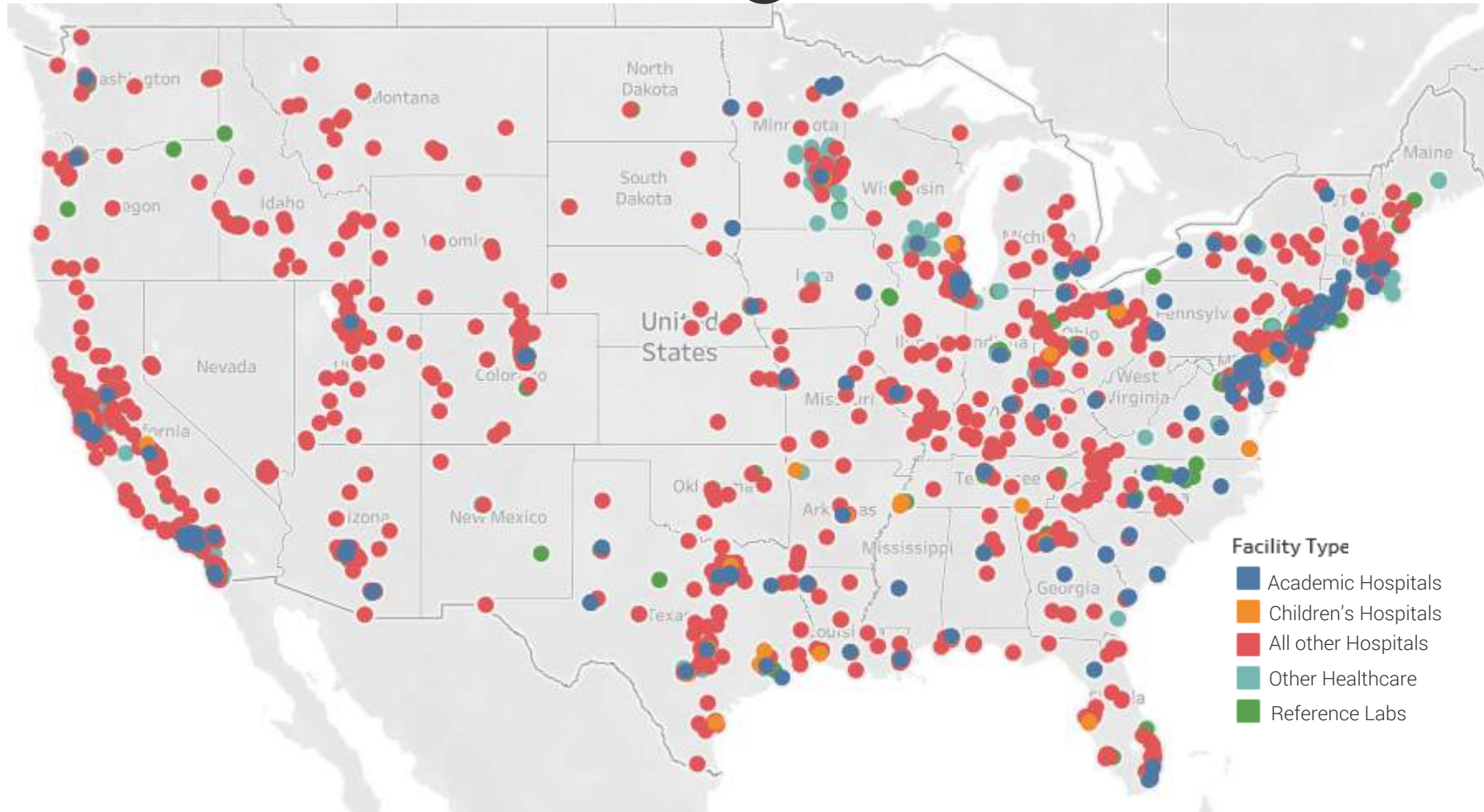
- Blood Services
- Immunohematology Reference Lab (IRL)
- Transfusion Services

ARUP INSTITUTE FOR CLINICAL & EXPERIMENTAL PATHOLOGY®

- Research and Development
- Specialized Technologies and Manufacturing

3,000+ Hospital Clients | serves 50 states, 50%+ of academic/pediatric institutions

National Coverage



<https://bi.aruplab.com/#/views/Clientbytype/Sheet1?iid=2> (2020 Jan data)

Collaboration & Sharing of Knowledge

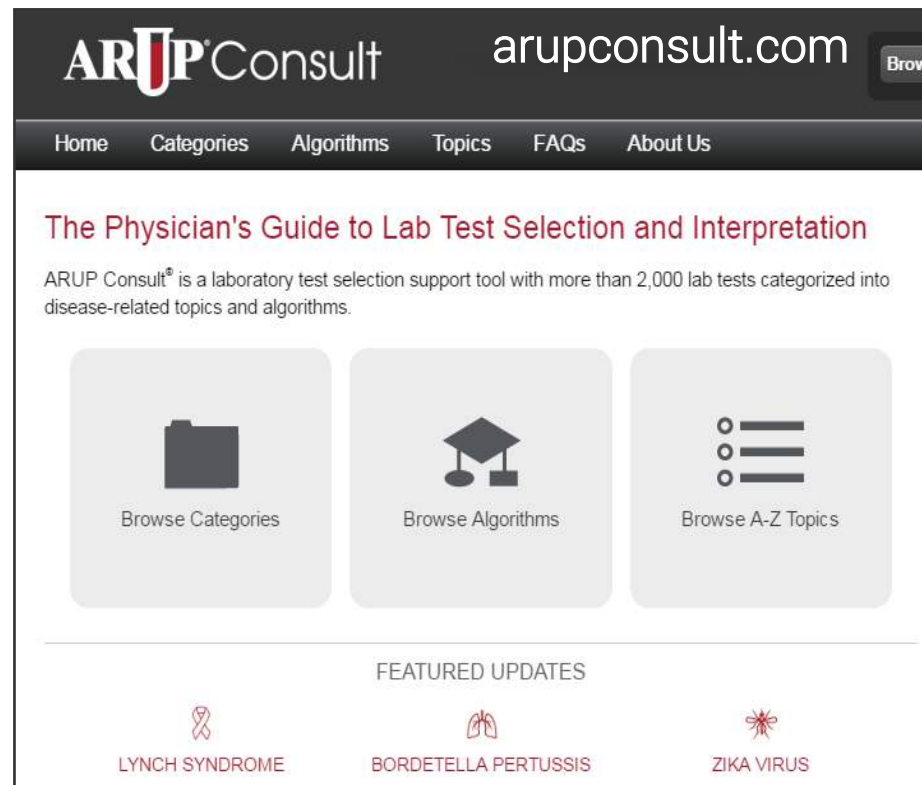
We believe in collaborating, sharing knowledge, and contributing to laboratory science in ways that provide the best value for the patient.



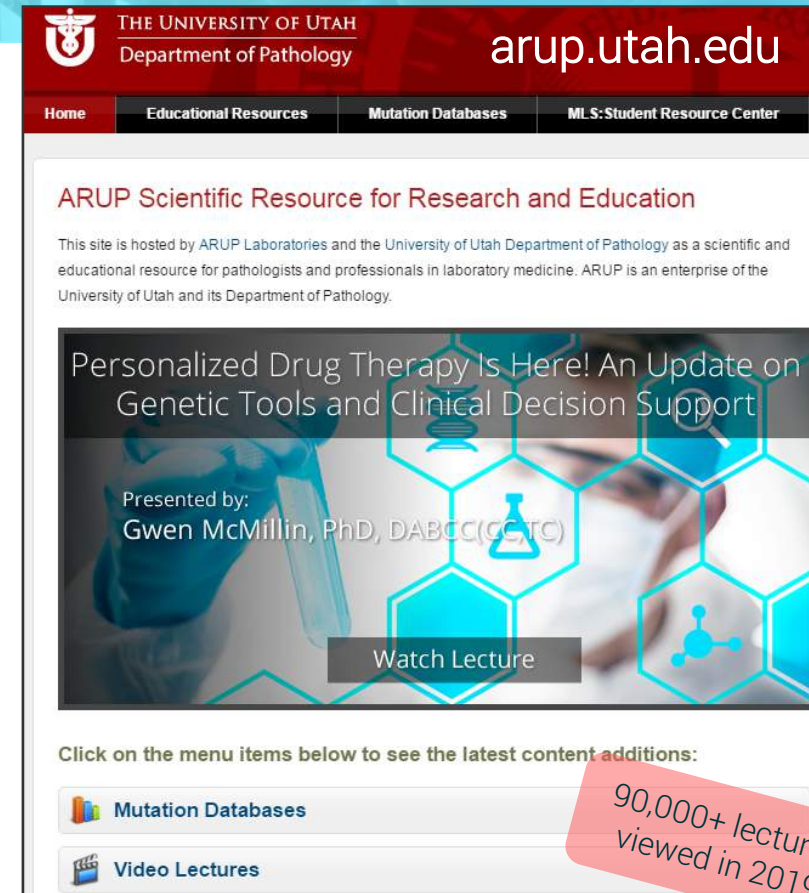
Collaboration & Sharing Knowledge

Online Education & Genetic resources

Guide for Physicians - curated by ARUP



The screenshot shows the ARUP Consult website. The header includes the ARUP Consult logo and the URL arupconsult.com. A navigation bar contains links for Home, Categories, Algorithms, Topics, FAQs, and About Us. The main content area features the title "The Physician's Guide to Lab Test Selection and Interpretation" and a description of the tool. Below this are three large buttons: "Browse Categories", "Browse Algorithms", and "Browse A-Z Topics". At the bottom, a "FEATURED UPDATES" section highlights "LYNCH SYNDROME", "BORDETELLA PERTUSSIS", and "ZIKA VIRUS" with corresponding icons.



The screenshot shows the ARUP Scientific Resource for Research and Education website. The header includes the University of Utah Department of Pathology logo and the URL arup.utah.edu. A navigation bar contains links for Home, Educational Resources, Mutation Databases, and MLS: Student Resource Center. The main content area features the title "ARUP Scientific Resource for Research and Education" and a description of the site. Below this is a large banner for "Personalized Drug Therapy Is Here! An Update on Genetic Tools and Clinical Decision Support" presented by Gwen McMillin, PhD, DABCC(C,TC). A "Watch Lecture" button is visible. At the bottom, a section titled "Click on the menu items below to see the latest content additions:" lists "Mutation Databases" and "Video Lectures".

90,000+ lectures
viewed in 2019



Molecular Diagnosis of COVID-19 infection

Chronology of COVID-19 Molecular Diagnosis in the US

Nov 2019	COVID-19 first reported in Wuhan, Hubei Province, China
Early-Mid February	First cases reported COVID-19 in the US
Mid February	CDC declares national emergency; FDA assumes control and regulation of molecular diagnostic testing within US
Mid-Late February	CDC distributes diagnostics testing kits to public and state labs. Specificity issues found with CDC test. Test has to be remade.
Late February	FDA publishes relaxed criteria for approval of COVID-19 molecular diagnostic testing performed by academic and commercial labs under Emergency Use Authorization (EUA) path. ARUP begins validation of assays.
Mid March	ARUP begins offering two EUA approved tests (Hologic and Roche by RT-PCR) for molecular diagnosis of COVID-19 infection.

Hologic Panther-Fusion System



Hologic's website

- High-throughput (~1,100 tests/day)
- Random access instrument
- Same instrument used for viral respiratory panels
- ARUP had two – bought two more
- SARS-CoV-2 test:
 - LOD: ~1,000 copies/mL
 - Specificity= 100% (96.6% - 100%)
 - Sensitivity= 100% (94.7% - 100%)
- Performance verified by ARUP

Roche Cobas 6800 System



Roche's website

- High-throughput (~1,400 tests/day)
- ARUP bought one 6800 system (as back-up)
- SARS-CoV-2 test:
 - LOD: ~250 copies/mL
 - Specificity= 100% (96.3% - 100%)
 - Sensitivity= 100% (92.9% - 100%)
- Performance verified by ARUP

Molecular Testing for COVID: ARUP Summary

- As of early May, ARUP has performed 100,000+ molecular diagnostics tests for all the US (~50% of all testing done for Utah)
- ARUP has provided 200,000+ collection supply kits (swabs, virus media) to hospitals around the country
- Current ARUP capacity is ~5,000 tests/day for molecular diagnosis of COVID-19
- ARUP is building to capacity to offer 7,500 tests/day

THE IMPORTANCE OF ANALYTICAL SENSITIVITY

- Molecular methods are highly specific but the ability to detect the virus when present varies due to different analytical sensitivities (Limit of Detection; LOD)
- Four hospital systems in Utah perform 8 different assays
 - » Six central lab assays: Roche, Hologic, Thermo, Quidel, Co-Diagnostics, & CDC
 - » Two rapid point-of-care assays: Biofire, Cephiad
- ARUP completed a comparison study to determine LODs for each method
- Results show >20-fold difference in analytical sensitivities among different assays. Results are being summarized and will be published soon.
- These results, along with results of the COVID-19 seroprevalence study in the state of Utah, will help to determine the false negativity rate of each method for diagnosis of infection in patients with low viral load.
- Critical information for returning to work decisions.

SUPPLY CHAIN CHALLENGES

- One of the biggest challenge for laboratories has been supply chain - everyone is competing for the same supplies
- The biggest viral media producer in the world (Copan) is located in Italy – shut down for over a month
- The US government took over the distribution and allocation of supplies
 - Instrumentation for testing
 - Testing kits and reagents
 - Swabs and media for collection
 - Personal protective equipment, etc.
- ARUP validated alternative viral transport media and investigated 3D printed swabs to become less vulnerable to supply chain allocations

Saliva Sampling for Molecular Testing?



DNA Genotek website

- Deep nasopharyngeal sample has the highest sensitivity for diagnosis – preferred sample
- Mid-turbinate and oropharyngeal sampling are alternative - lower testing sensitivity
- Saliva has been shown to work for DNA and RNA amplification for genetic and microbial testing
- ARUP is working to validate saliva sampling for molecular diagnosis of COVID-19 using various saliva collection devices
- Collaboration with Intermountain Healthcare and the University of Utah



Serological (antibody) testing for COVID-19 infection

Chronology of COVID-19 Serology in the US

Mid-Late March	FDA publishes loose guidance for development of serological testing for COVID-19 antibodies within US.
Early April	FDA approves two pathways for authorization of serological testing by laboratories within US. • Submission by manufacturers for review and approval for EUA by FDA (<15 tests given EAU as early May) • Letter by manufacturers to FDA informing intention to use (160+ tests approved by this pathway as early May) List of authorized tests can be found in FDA website.
Mid-April	ARUP begins offering two EUA approved IgG serological tests (Abbott by CIA and EuroImmune by ELISA) for antibody detection.
Early May	FDA requires antibody testing manufacturers to provide accuracy data within 10 days of use.

Abbott's Architect i2000sr system



Abbott's website

- High-throughput
4,000 tests/day/instrument
- ARUP rented **six instruments**
- SARS-Cov-2 IgG qualitative test targets nucleocapsid protein:
Specificity= 99.63% (99.05, 99.90)
Sensitivity= 100% (95.89, 100.00) at 14 days post-symptom onset (both verified by ARUP)

Verification performed using 200+ samples pre-pandemic; samples positive for other coronavirus and common viral infections; and samples from SARS-CoV-2 PCR+ patients

Agility's Dynex ELISA System



Agility's website

- High-throughput
- ~2,500 tests/day/instrument
- ARUP had **four** – purchased **two** more
- EuroImmune IgG semiquantitative test targets S1 domain of spike protein:
 - Specificity = 99% (98.7, 99.3)
 - Sensitivity = 100% (93.14, 99.62) at 14 days post-symptom onset (both verified by ARUP)

Verification performed using 200+ samples pre-pandemic; samples positive for other coronavirus and common viral infections; and samples from SARS-CoV-2 PCR+ patients

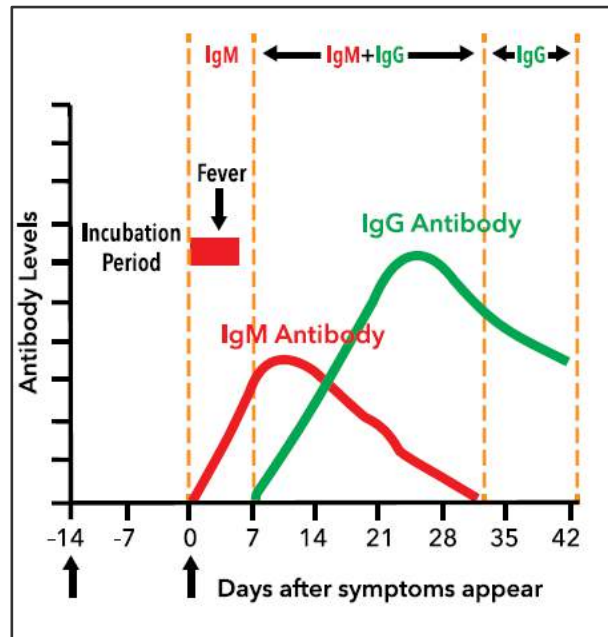
Antibody Response to Prior Coronavirus Infections

What is Known So Far

- Antibodies are produced against current 4 human endemic coronavirus, as well as SARS-CoV-1 and MERS
- Antibodies against coronaviruses produce immunity
- Antibody responses decrease overtime although can last over one year or more in small subset of individuals
- Antibody responses to coronaviruses directly correlate with symptoms severity
- There is evidence of some cross-reactivity of immunity among coronavirus antibodies

Huang et al., in: www.medrxiv.org; doi:10.1101/2020.04.14.20065771v1

Early Findings about Antibody Responses to SARS-CoV-2



BioMedomics COVID-19 Brochure

Long et al., Nature Medicine, 2020
Okba et al., Emerg Infect Dis, 2020

- IgM antibodies are produced 5-7 days after COVID-19 symptoms
- IgG antibodies are produced 7-10 days after symptoms with most patients showing antibodies at day 14
- IgA antibodies are also produced early but sensitivity is relatively poor
- Early studies in China have shown that IgG antibodies are neutralizing *in vitro*
- Preliminary clinical studies have shown that up to 30% of patients with COVID-19 infection do not develop IgG antibodies or have low titers
- IgG antibody levels appear to correlate with severity of disease
- Older individuals have higher IgG antibody response, likely due to higher severity of disease
- Too early to know about duration of antibody responses

Interpreting IgG Antibody Results

Presence of IgG antibody:

- Indicates exposure to COVID-19 if test is specific
- Does not indicate protective immunity – pending ongoing studies
- Does not inform infection status:
 - patient may have cleared infection
 - patient may still be infectious for several days after seroconversion if IgG test done too early
- Cannot be used to diagnose acutely ill patients
(only molecular tests are to be used to diagnose disease)

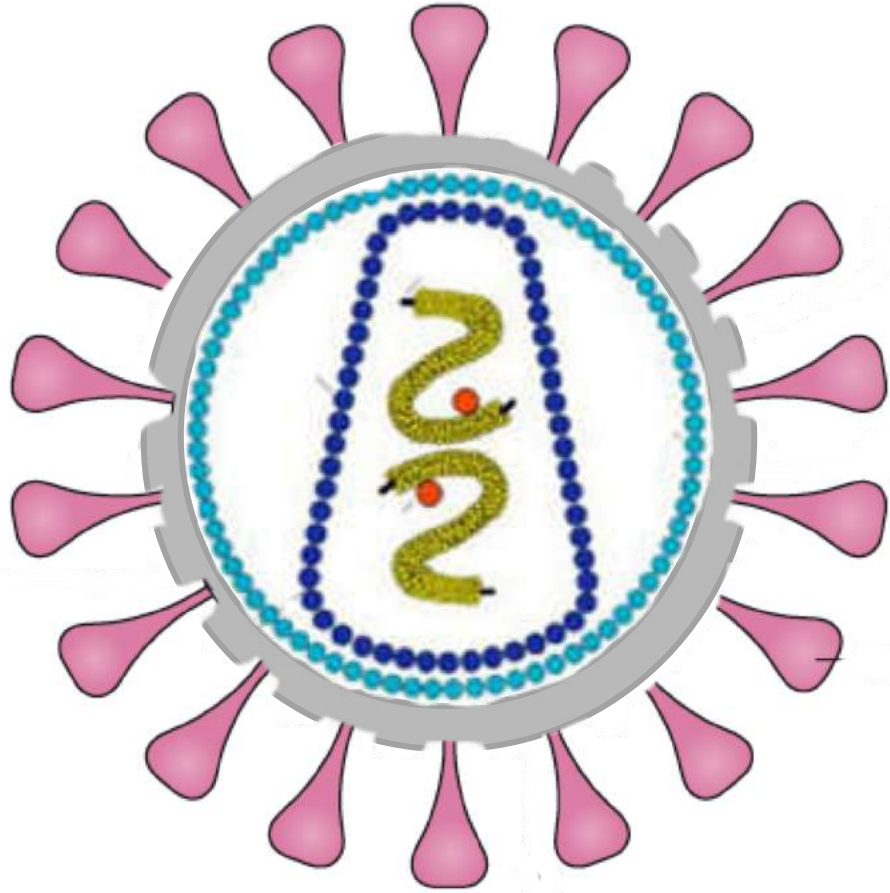
FDA is contemplating the need to test for IgG using 2 different assays targeting different proteins to increase PPV in low prevalence settings

How to Determine if IgG Antibodies are Protective?

- **Neutralization assays** using live culture of SARS-CoV-2 is the preferred method to determine if IgG antibodies are protective
- Most routine viral culture testing in the US has been suspended due to risk of virus growth in conventional viral media
- Few laboratories in the world are culturing SARS-CoV-2 due to risk of contagion
- An alternative is to use psedotype virus for neutralization assays

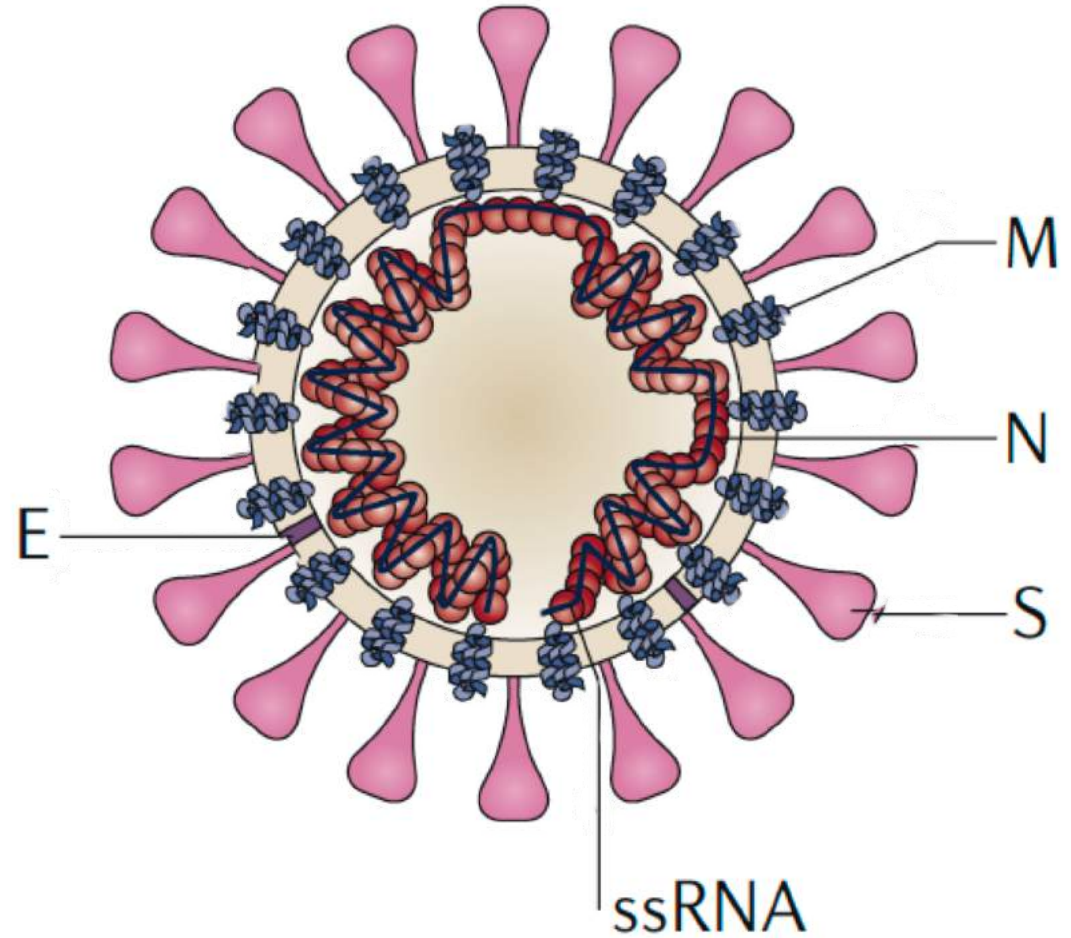
Huang et al., medRxiv.org doi: 10.1101/2020.04.14.20065771v1

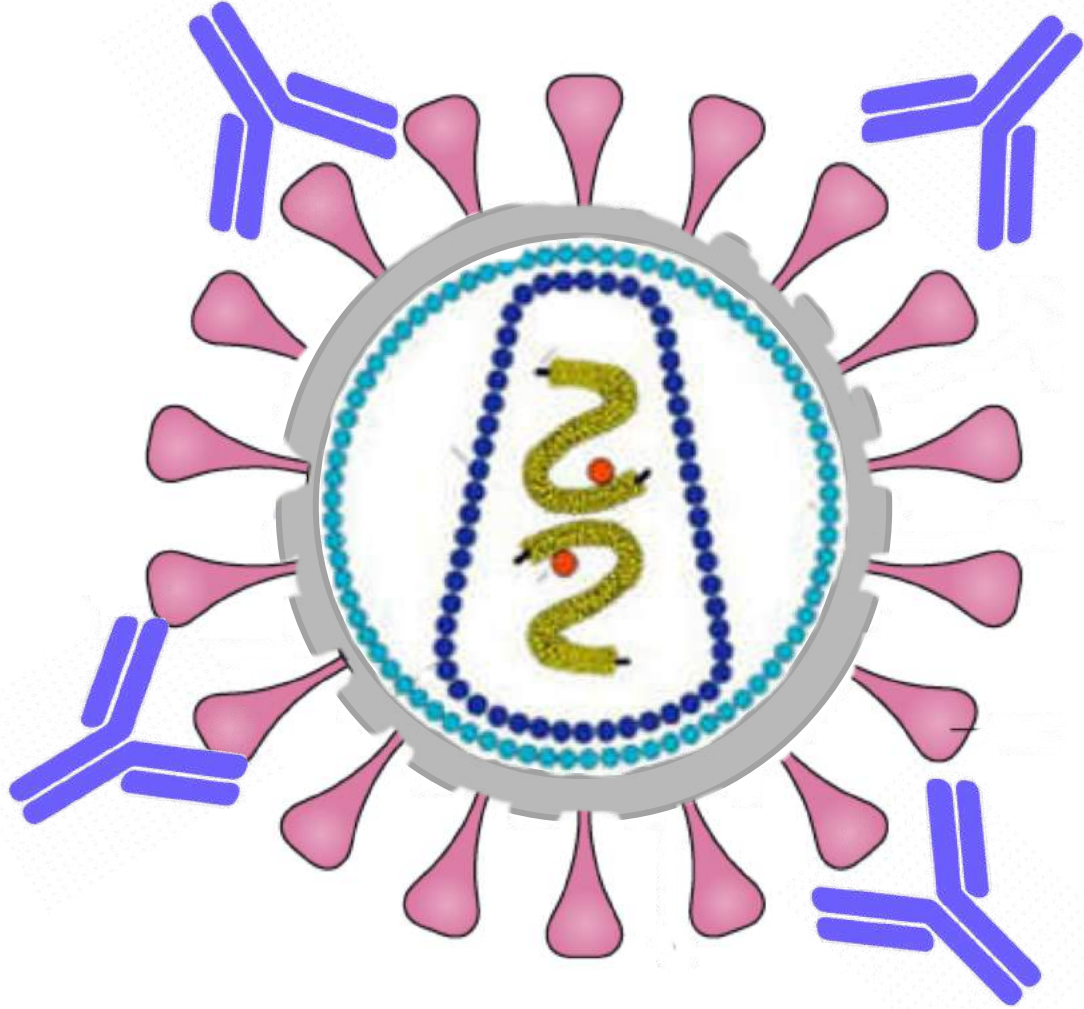
HIV-1



pseudo SARS-CoV-2

SARS-Cov-2

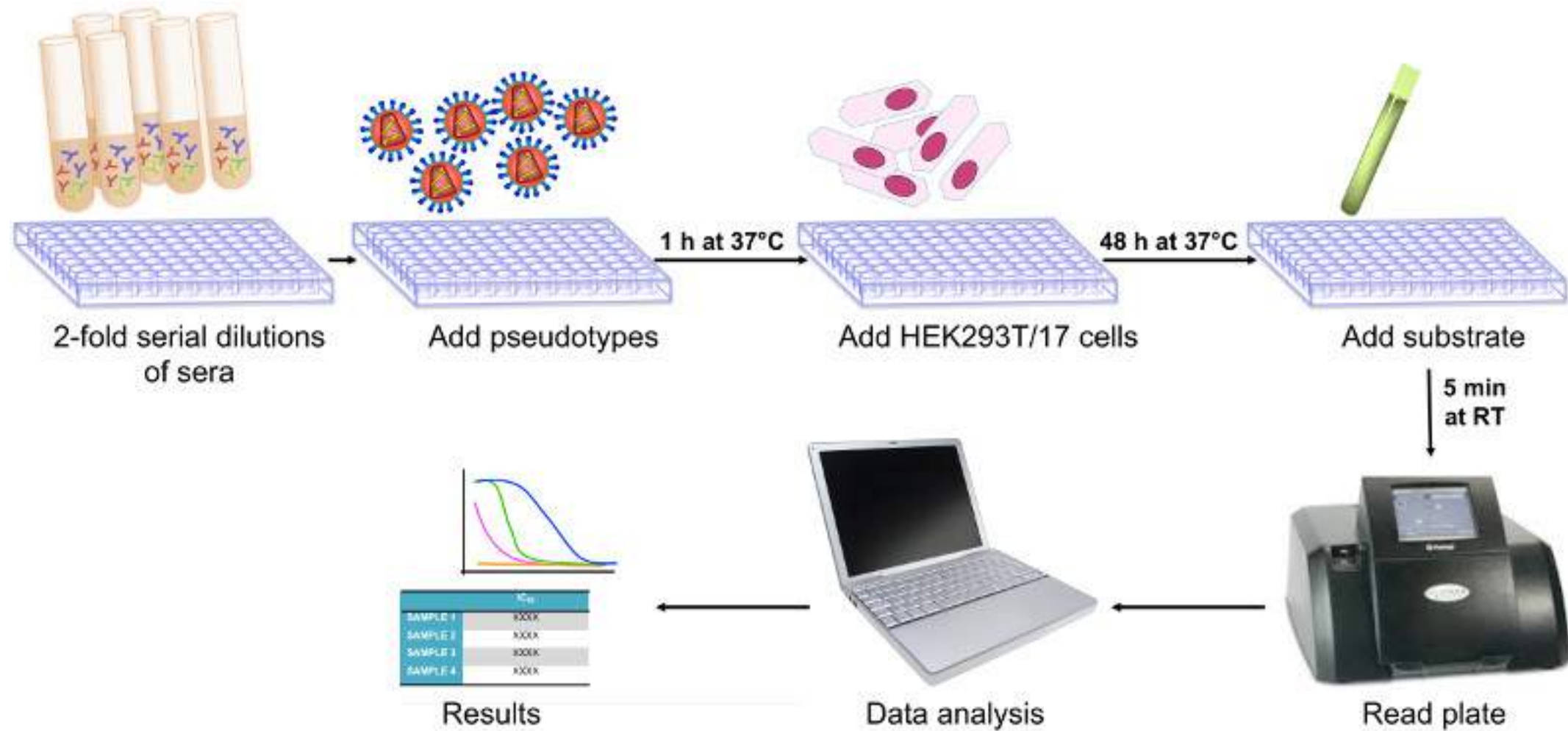




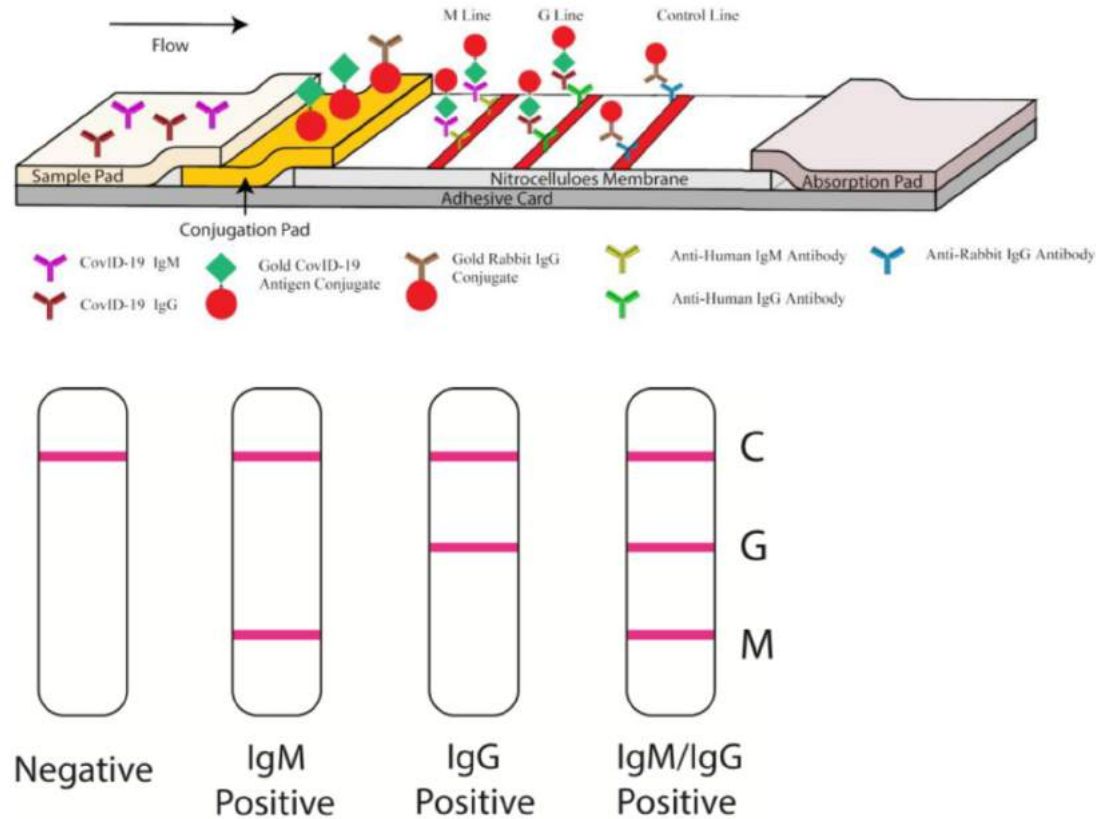
SARS-CoV-2 pseudotype

- Mimics receptor binding and entry
- Safe for work in BSL2+
- Uses:
 - Antibody neutralization testing
 - Selection of plasma donors
 - Emergency and duration of NAbs
 - Vaccine testing

Neutralization assay



Issues with Rapid Testing for Antibodies



Augurux website

- Hundreds of companies are offering rapid-antibody testing by lateral flow immunoassay. Most of the companies didn't exist 4-5 months ago. No track record of producing accurate and precise testing.
- Preliminary results show lateral flow assays have sensitivity vary between 65-85% and specificity between 85-95%
- At this point, it is risky to use rapid antibody testing using lateral flow assays – better to use central laboratory testing at this stage

Adams et al., medRxiv.org doi: 10.1101/2020.04.15.20066407
Whitman, et al., medRxiv.org doi: 10.1101/2020.04.25.20074856

How to perform efficient, patient-friendly and reliable point-of-care blood collection for antibody testing?



Microcapillary collection – Tasso website



Microcapillary collection – Seventh Sense website



Dry blood spot collection – Spot On Sciences website

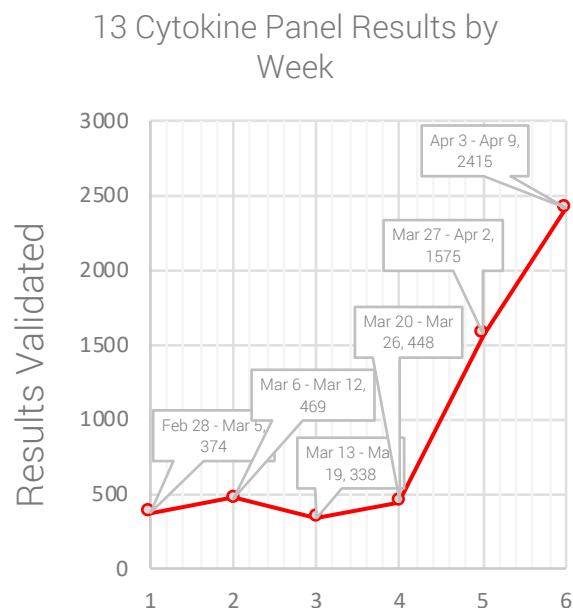
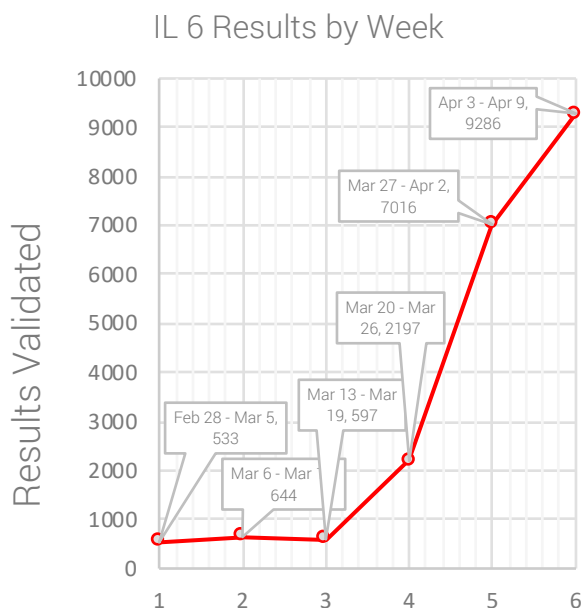
- It is expected that antibody determination will require repeated testing
- Venous blood collection is impractical and not patient-friendly at work or at home settings
- ARUP is exploring alternative blood collection devices used for other applications (newborn screening, glucose, Hb1c, etc.)
- Several collection methods are being compared to conventional venous blood collection for sensitivity of antibody results



■ Cytokine testing in COVID-19

IL-6/Cytokine Panel Testing at ARUP Laboratories

- In-house developed tests using Luminex based immunoassay
- As early May, ARUP has performed 50,000+ IL-6/cytokine tests (20-fold increase) since COVID-19 pandemic



Why Test for Cytokines in COVID-19 patients?

THE CORONAVIRUS CRISIS

Why Some COVID-19 Patients Crash: The Body's Immune System Might Be To Blame

April 7, 2020 - 9:00 AM ET
Heard on Morning Edition



Cancer Immunotherapy for COVID-19: 'Extraordinary Times Call for Extraordinary Measures'

BRIELLE BENYON
Thursday, March 26, 2020



According to research published last week in *the Lancet*, there is a subgroup of patients with the virus who might have a cytokine storm syndrome.² Additionally, an article from European Radiology states that patients with COVID-19 tend to have high levels of C-reactive protein (CRP) and IL-6.³

<https://www.npr.org>

<https://www.oncnursingnews.com/web-exclusives/cancer-immunotherapy-for-covid19>

The Coronavirus Patients Betrayed by Their Own Immune Systems



<https://www.nytimes.com/2020/04/01/health/coronavirus-cytokine-storm-immune-system.html>

Why Test for IL-6 in COVID-19 patients?

- Used as marker for monitoring of “**cytokine storm**” – serious complication seen in a subset of patients with hyper-immune response to infection
- Therapies targeting IL-6 are approved to treat “cytokine storm”/cytokine release syndrome (CRS) in cancer patients receiving CAR T-cell therapy
- Preliminary evidence suggests that IL-6 targeting therapies are efficacious in patients with severe COVID-19, with multiple clinical trials currently underway



<https://www.cusabio.com/COVID-19-Cytokine-Storm>



■ Plasma Transfusion for COVID-19

COVID-19 Convalescent Plasma (CCP)

- No proven options for prophylaxis; only one for treatment (Remdesivir)
- CCP collected from individuals after resolution of infection and development of antibodies
- Potential uses
 - » May prevent infection / blunt severity after recent exposure
 - » Bridge before vaccine?
- Collection must meet FDA safety, purity

What do we know about safety and efficacy?

- SARS1 2003:
 - » 80 patients in Hong Kong → CCP before day 14 associated with higher rate of discharge by day 22
 - » Other small case series
- MERS 2012:
 - » Small case series
- COVID-19:
 - » 10 severe patients in China → no serious adverse effects, symptoms improved 1-3 days after transfusion
 - » 7 RNA-emic patients → temporarily associated with undetectable viral loads
 - » 5 critically ill patients in China → all improved
- Study design limitations, but suggest safe, may be efficacious
 - » Randomized clinical trials are needed

Bloch et al. J Clin Invest. 2020.
Shen et al. JAMA. 2020.

CCP Collection at ARUP Blood Services

- ARUP Blood Services began collection of CCP from eligible donors
- Apheresis technology to maximize potential benefit
 - » Greater plasma volume per donation
 - » Return RBCs to donor during apheresis collection
- Currently, CCP can be given to patients for compassionate use
- Therapy is unproven, so participating in studies is important
- ARUP is participating in a randomized placebo controlled post-exposure prophylaxis multicenter clinical trial run by Johns Hopkins
 - » Has FDA approval
 - » Targeting HCW or family member with high risk exposure as donors



■ On-going research in COVID-19 by ARUP Laboratories

Prevalence Studies are Critical for Planning Future Surveillance Programs of COVID-19

Heath and Economic Recovery Outreach (HERO) Study

- Collaboration between the University of Utah Medical and Business Schools, ARUP, and the State of Utah with mobile collections over the whole state of Utah
- SARS-CoV-2 PCR and serology testing for 10000 individuals in Utah randomly selected

The goals are to identify:

- Current rate of infection in Utah and changes in infection rates including undetected and asymptomatic cases
- Range of symptoms for individuals with COVID-19
- Improvements in detection and tracing rates

COVID-19 and ARUP's Clinical Trials

ARUP is well-positioned to partner with sponsors to perform COVID-19 related testing in support of clinical trials. Below are 2 high profile trials that we are doing:

UU/IHC Hydroxychloroquine Study

- SARS-CoV-2 PCR testing for 400 outpatients and their adult household members over 15 timepoints (15,000 tests in total)
- Objective is COVID-19 viral shedding to determine efficacy of hydroxychloroquine treatment

CDC-sponsored COVID Evaluation of Risk for Emergency Departments (COVERED) Project

- SARS-CoV-2 PCR and ELISA serology testing for 1600 healthcare workers at 21 sites nationwide over 7 timepoints (22,400 tests in total)
- Objective is to estimate risk of acquisition of COVID-19 by healthcare workers during emergency care and to identify risk factors associated with transmission

Concluding remarks

- COVID-19 is the biggest event in our lifetime
- Our lives will probably never be the same again
- WE (physicians, scientists) have a responsibility to lead and influence decisions
- We must publish everything, not only positive but also negative results. Negative results are as important during times like this
- Regulations for clinical human trials for treatment and vaccines have been relaxed. We must be careful to protect patients and not to overstate results
- It is great to have a purpose in life during times like this

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A nonprofit enterprise of the University of Utah and its Department of Pathology