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COVID–19
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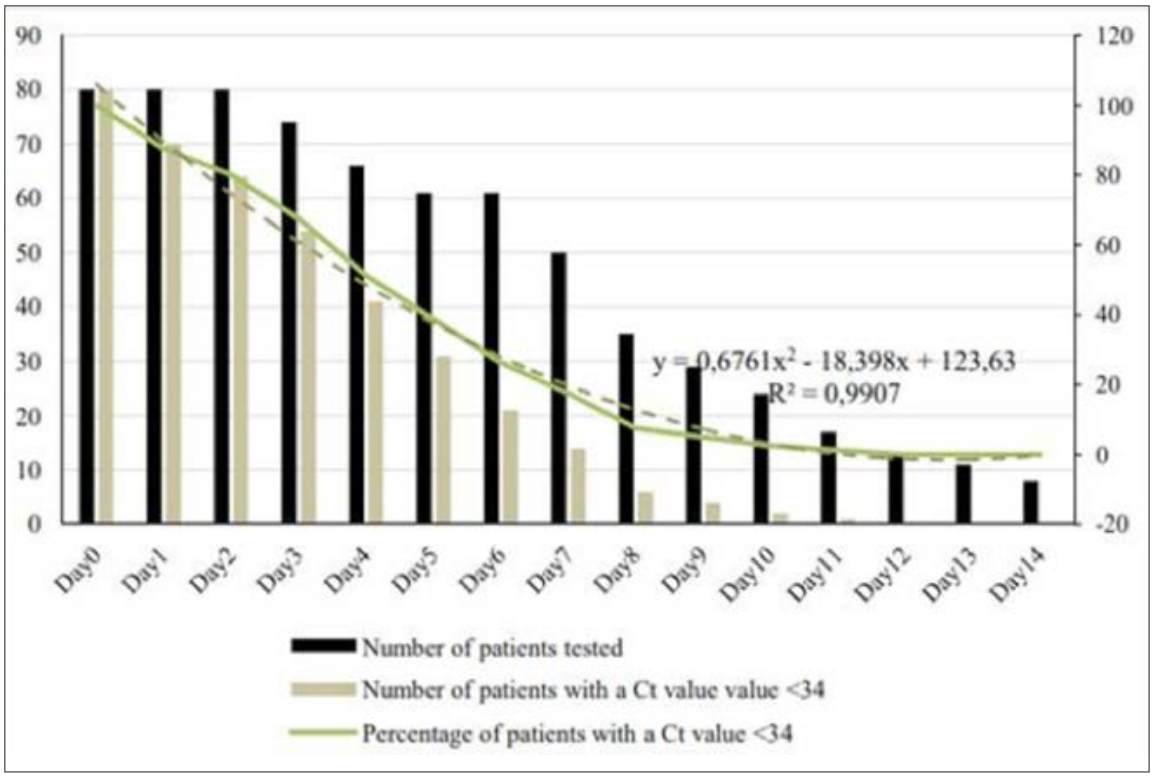
EDUCATIONAL FORUM

The role of PCR, IgM and IgG levels in the diagnosis of COVID-19 infection[1]

Currently, most COVID-19 testing in the U.S. is via the anterior nasal swab or nasopharyngeal PCR test. This represents the current gold standard for testing. The sensitivity of the nasal swab PCR test has been reported to be in the range of 70-90%. Part of this low sensitivity is related to the intrinsic complexity of the assay and part related to the fact the viral detection in the nasopharynx, particularly in mild to moderate cases, declines quickly after infection. A rapid fall of nasopharyngeal viral load tested by qPCR was noted in a French study, with 83% negative at Day 7, and 93% at Day 8. The below graph illustrates the decline in PCR positivity as a function of duration of infection in non-hospitalized patients. Importantly, asymptomatic carriers seem to carry very low levels of virus and as such, may fall below the limit of detection of the PCR assay and therefore have a false negative PCR. The current estimate of asymptomatic transmission in the U.S. is 25%. Moreover, in two studies looking at populations in China and Singapore, the rate of pre-symptomatic transmission of infection was 48%–62%.



IgM and IgG antibody assays are under rapid development and are now being marketed to providers as POC tools using fingerstick samples. Importantly, these have not yet been FDA approved and have not been released under the emergency use authorization (EUA). As you can see from the below graph, shared in the last version of this Forum, the IgM titer on average becomes detectable around day 6–7. However, because there are several benign coronaviruses currently in

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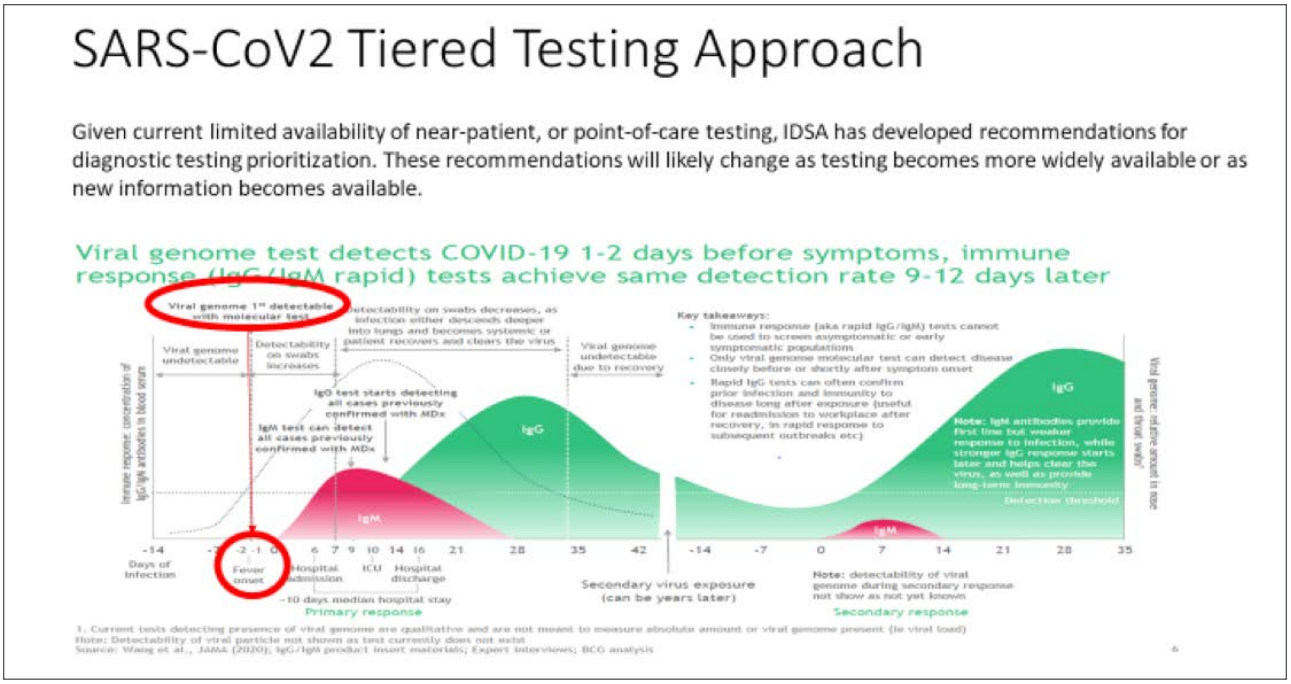
circulation due to the recent URI seasons, there can be cross reactivity and therefore cause false positive rates with the IgM assay. The IgG assay has far fewer false positives and IgG levels rise only a few days later than IgM. IgG therefore may be a more reliable measure of recent infection. In some individuals, IgG titers will become positive at around day 7 when the PCR positivity is declining. Therefore, the combination of PCR plus IgG will increase the sensitivity of COVID-19 detection, possibly to the 85% range. We have not yet validated the reliability of the antibody assays despite the fact that these are being widely marketed, and as noted, are neither FDA approved nor released under the EUA. Currently therefore, a rational approach to testing in clinical practice is as follows:

- Continue to use the IDSA recommendations for testing Tier 1 and 2 patients using nasal PCR as noted below.
- When antibody assays have been validated, they will be most useful in the following scenarios:
  - Testing of HCP for safe return to work
  - Testing of patients with clinically suspected COVID-19 infections who have negative PCR assays, when the confirmation of diagnosis will change clinical management
  - Surveillance testing of the general population to study the epidemiology of the COVID-19 pandemic
  - To confirm immunity in patients who have recovered or may have had asymptomatic infection. This will become increasingly important as a method to prevent recurrent outbreaks as we begin to wind down social isolation.



IDSA definitions

Tier 1
Critically ill patients receiving ICU level care
Individuals with fever or signs/symptoms of a lower respiratory tract illness who are also immunosuppressed
Individuals with fever or signs/symptoms of a lower respiratory tract illness who are critical to pandemic response, including health care workers, public health officials and other essential leaders
Any person, including health care workers, with fever or signs/symptoms of a lower respiratory tract illness and close contact with a laboratory-confirmed COVID-19 patient within 14 days of symptom onset or history of travel
Tier 2
Hospitalized (non-ICU) patients and long-term care residents with unexplained fever and signs/symptoms of a lower respiratory tract illness
Tier 3
Symptomatic patients in outpatient settings with co-morbid conditions including diabetes, COPD, congestive heart failure, age >50, immunocompromised hosts among others. Given limited available data, testing of pregnant women and symptomatic children with similar risk factors for complications is encouraged
Tier 4
Community surveillance as directed by public health and/or infectious diseases authorities

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Surgical face masks reduce aerosolized COVID-19 during natural coughing

The Centers for Disease Control and Prevention recently recommended that all individuals use a cloth face covering in settings where social distancing cannot be maintained consistently (e.g., grocery stores and pharmacies), especially in regions where COVID-19 transmission is substantial.[1] The aim of the recommendation was to help prevent the spread of virus among infected individuals who are asymptomatic and may not know that they are contagious. The CDC website provides instructions for the home construction and cleaning of cloth face coverings.[2] Surgical face masks and respirators should be reserved for healthcare workers and other medical first responders.

A recent study[3] explored the efficacy of surgical face masks in preventing aerosolized and droplet viral shedding among symptomatic patients with acute respiratory illnesses. The analysis focused on 111 patients with COVID-19 (n=17), influenza (n=43), and rhinovirus (n=54) infections. Patients co-infected with more than one virus were included. Following randomization to wearing or not wearing a face mask, participants were instructed to breathe normally for 30 minutes during sample collection while natural coughing was allowed. COVID-19 infections caused more coughing (average 17 coughs per 30 minutes) than infections with influenza or rhinovirus. Some patients volunteered to provide a second breathing sample in the alternate face mask group. Among 10 patients with coronavirus but without face masks, 3 (30%) had virus detected from respiratory droplets and 4 (40%) had virus detected from aerosols. In contrast, none of the 11 patients who wore face masks had coronavirus detected from droplets or aerosols. A significant difference was found between masking and not masking for aerosol detection (P=0.04), but statistical significance was not reached for droplet detection (P=0.09). Surgical face masks also decreased influenza detection from droplets but not aerosols; no differences were found with masking and rhinovirus shedding.

The study demonstrates that (A) COVID-19 virus can be detected from droplet and aerosol samples generated from coughing and that (B) masking significantly decreases aerosolized viral shedding. Although a significant difference was not seen from droplet samples, it must be emphasized that coronavirus was not detected from any respiratory samples when patients wore masks. The low number of study participants with COVID-19 was a limitation, especially with a subset not coughing during the 30-minute sample collection.

Efficacy of the cloth face covers recommended by the CDC cannot be extrapolated from this study. Using a face covering could paradoxically lead to added transmission if it diverts attention from more fundamental infection control measures such as hand washing.[4] The recommendation for public use of face covers needs to be included in a larger framework of patient education about COVID-19 control and prevention.

Patients with severe COVID-19 infections have higher viral loads than patients with milder disease[5]

Patients hospitalized with COVID-19 were stratified as severe or mild disease and serial viral counts were compared between groups. The authors defined severe disease as one or more of the following:

1. Respiratory distress (≥30 breaths per min)
2. Oxygen saturation ≤93% at rest
3. Low partial pressure of arterial oxygen
4. Severe disease complications (e.g., respiratory or other organ failure, mechanical ventilation, septic shock)

Patients with mild disease had none of the features listed for severe disease. Patients with severe disease had mean **viral loads** 60 times higher than those with mild disease. Milder cases had earlier viral clearance, with 90% repeatedly testing negative 10 days after symptom onset. In contrast, all patients with severe disease continued to shed virus beyond 10 days. These results suggest that early measures of viral load might have prognostic value. Additionally, there results have implications for the management both of our employees and providers who have contracted COVID-19 infection as well as the discharge follow up of these severely infected patients.

- **Employees and providers –** these results support our current return to work policy in non-severely affected individuals. It is possible that a small fraction of these individuals could still be shedding virus, hence our return to work precautions that include masks and gloves for all patient contacts.
- **Severely ill patients post discharge –** because these patients are likely to still be shedding virus at discharge, they all need to practice careful home quarantine practice and their first follow up appointment should be at the FURI clinic. Once they have clinically stabilized, subsequent follow up visits will best be held using televideo capability.

Preliminary data suggest mild neonatal COVID-19 infections and infrequent vertical transmission

A pandemic of the novel coronavirus (COVID-19) has led to infections of pregnant women, but little is known about the risks to newborns. Zeng and colleagues[6] report clinical features from a cohort of neonates born to mothers with laboratory-confirmed COVID-19. Among 33 neonates, 3 (9%) had positive nasopharyngeal and anal swabs. Each of the three had radiographic signs of pneumonia; 2 had fevers; 2 had leukocytosis. One of the patients was born prematurely at 31 weeks, developed signs of sepsis with a suspected Enterobacter infection, and required mechanical ventilation. He improved with antibiotic treatment. Each of the 3 patients

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had positive nasopharyngeal and anal swabs for COVID-19 on days 2 and 4 of life with negative swabs by days 6 or 7. Specific longer-term outcomes were not reported, but were described as favorable.

Given the infection control measures implemented during deliveries, the authors presumed that the source of neonatal COVID-19 was maternal, but antibody testing was not performed. A neonate born to a mother with COVID-19 was reported to have elevated IgG and IgM antibodies at 2 hours of life.[7] Since IgM antibodies do not cross the placenta, in utero infection was suspected. However, the child remained symptom free, and serial nasopharyngeal and anal swabs were negative.

In a separate study published in The Lancet, nine women presented late in pregnancy with COVID-19 pneumonia.[8] All were delivered by caesarian section in their third trimester. None of the patients developed severe COVID-19 pneumonia or died. Nine livebirths were recorded. All nine livebirths had a 1-min Apgar score of 8–9 and a 5-min Apgar score of 9–10. Importantly, amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples from six patients were tested for SARS-CoV-2, and all samples tested negative for the virus.

Lastly, a study published Monday in the American Journal of Obstetrics and Gynecology looked at 43 patients presenting to New York hospitals in their third trimester either with symptomatic infection or detected on screening at admission to the obstetrics unit. Ninety percent of the women ultimately developed symptoms but only one was severely symptomatic requiring supplemental oxygen, and none required ICU care or intubation. Eighteen babies were delivered during the study period and all had normal Apgar scores. There were no documented infections in the neonates, including the ten that were vaginally delivered.[9]

Taken together, these data, although limited, suggest infrequent vertical transmission of COVID-19 infection with the more likely mechanism of infection in the three above cases being related to vaginal delivery. Overall, the clinical course in the third trimester of pregnancy seems to parallel other infected young adults. With respect to the neonates, the incidence of infection is low and might be prevented by caesarian section.

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Kenneth Roy Cohen, MD, FACP | *Chief Medical Officer*

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He has successfully developed and reported numerous clinical quality studies in primary care, including tobacco cessation, osteoporosis, asthma, diabetes, hypertension, and ischemic vascular disease. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He has served as Chief Medical Officer since 1995. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA | *Senior Medical Director*

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD | *Senior Clinical Practice Performance Consultant*

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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