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COVID–19
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EDUCATIONAL FORUM

Update on the sensitivity/specificity and positive predictive value/negative predictive value of IgG levels for SARS-CoV-2

Few topics have generated as much confusion as this one. The confusion stems from the fact that even when a test has a moderately high specificity, when the prevalence of a disease in the population is low, the positive predictive value drops substantially. We can think of this in terms of Bayes' theorem as it applies to exercise stress testing. Overall, stress testing has an approximate 75% specificity for coronary artery disease. Consider these two scenarios:

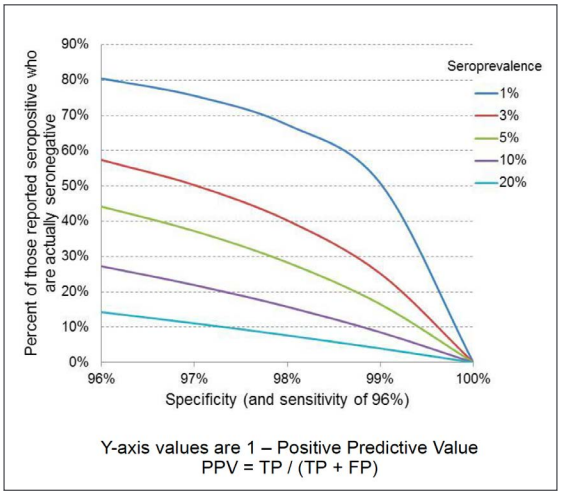
> **Scenario 1:** A 75-year-old with diabetes and tobacco use presents with reproducible exertional angina. Because the pretest probability of CAD in this patient is about 70% (i.e., CAD prevalence in a similar population), the positive predictive value of an abnormal stress test in this patient is 91%.
>
> **Scenario 2:** A 45-year-old female without risk factors presents with non-exertional chest pain. Because the pretest probability of CAD in this patient is about 5% (i.e., CAD prevalence in a similar population), the positive predictive value of an abnormal stress test in this patient is 20%. In other words, for every five positive stress tests, one will be a true positive and four will be false positives.

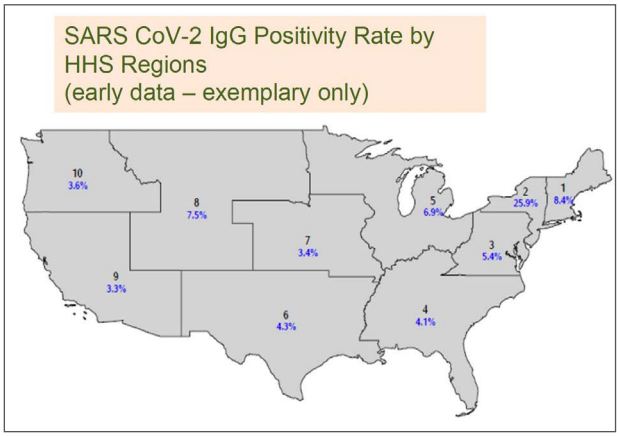
This exact same scenario needs to be applied to our COVID-19 IgG testing. Because the prevalence of COVID-19 across the United States varies from 26% in New York state, down to 3–4% for much of the country, the specificity of a positive IgG will vary enormously. This has very important implications since in much of the country a positive IgG may be no better than a coin toss in terms of whether it is a true positive or a false positive, and therefore we cannot assume prior infection based solely on the positive antibody test. Using the above analogy of the 75-year-old with diabetes and tobacco use, a positive IgG in someone with a recent bout of typical COVID-19 infection would have a high reliability and a low false positive rate, particularly in areas with higher prevalence rates. On the other hand, testing in asymptomatic individuals is a completely different situation. To illustrate the specificity, (in this case the false positive rate) of the IgG as a function of disease prevalence in different geographies, refer to the below pictorial.

Note that the regional percentages are only approximate and will change over time. The chart assumes a sensitivity of 96% and shows how the false positive rate starts very high rate and the rate declines to zero as the specificity moves from 96% up to 100% at varying community prevalence rates. Fortunately, our commercial lab assays through Quest and LabCorp have specificities of about 99.5%. However, even with this high specificity you can see how the false positive rate climbs quickly where the community disease prevalence rate is low. For example, at our current lab specificity of 99.5%, the false positive rate is still about 20% when the community prevalence is 3%. It is important that we have a firm grasp of this concept as it is very difficult for our patients to understand the limitations of antibody testing in these circumstances.

The below graphic is courtesy of Quest diagnostics.

IgG serology value for RTW is highly dependent on seroprevalence within the testing population





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An update to the COVID-19 vaccine development

Final containment of the COVID-19 pandemic will only result when we reach a level of herd immunity of an estimated 60–70% of the population. Ideally, this level of immunity will occur as a result of a vaccination program for the majority of the population. However, vaccine development typically requires 7–10 years. An ambitious timeline to develop a vaccine for COVID-19 in 12–18 months has been proposed. Such an ambitious program will require a completely new vaccine development process.[1]

Vaccine development typically occurs in a series of well-defined processes over a decade.[2] New methods in vaccine development use novel new platforms such as RNA- or DNA-based or recombinant-subunit vaccines and use of "viral-like particles." These can be more rapidly implemented.[3] As a result, a major vaccine development process is underway to meet an 18-month development timeline. It will be run in parallel rather than in a series of phase I trials progressing to phase III trials. This entails much more risk considering that in the typical vaccine development process, attrition of candidate vaccines is high and often reaches 90%.[4]

It is expected that vaccines will be successful in generating antibodies to major SARS-CoV-2 antigens. It is unknown if the generated immune response will be protective, what will be the length of immune protection and what will be the number of doses needed to generate an acceptable response.

There is also concern that a vaccine might exacerbate pulmonary inflammatory disease via an antibody enhanced immune response. Non-neutralizing antibodies or neutralizing antibodies at sub-optimal doses can lead to antibody-dependent enhancement of infection (ADE). ADE exacerbates diseases caused by feline coronavirus, MERS-CoV and SARS-CoV-1. ADE might thus also play a deleterious role in COVID-19. This could manifest clinically when certain individuals who were vaccinated and then exposed to viral infections, have a more severe course than those who were not vaccinated.

Despite all of these concerns and challenges, as of April 8, 2020 115 vaccine candidates have been identified, 78 of these are actively in development with 73 in exploratory or preclinical stages. Several of the most advanced vaccine candidates have entered clinical trials (Table1), including one vaccine about to launch a phase II trial. There are currently reasonable expectations that vaccines may be available by early 2021.[5]

Table 1. More advanced COVID-19 vaccine candidates

Company / candidate	Company location	Viral vector	Vector status	Antigen target	Phase 1	Phase 2
CanSino Biologic / Ad5-nCoV	BIBP	Adenovirus	Inactivated	Spike protein	Complete result NA	375 vac 125 control
Sinovac	BIBP	Adenovirus	Inactivated	Unk	Complete N=144	600 pts planned YTS
University of Oxford with AstraZeneca[6]	UK	Adenovirus	Unk	Spike	1102 pts	YTS
Inovio Pharma / INO-4800	US	DNA platform	None		Ongoing	YTS
Moderna[7] with NIAID / mRNA-1273	US	RNA platform	None		Ongoing	YTS
BioNTech with Pfizer	Germany	mRNA formats (4)	None	Various in 4 vaccines	200 pts planned	YTS

NA = not available; Unk = unknown; pts = patient; Vac = Vaccine; BIBP = Beijing Institute of Biologic Products; YTS = yet to start

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Remdesivir update

The use of remdesivir has attracted significant attention in the past couple of weeks. Although it does appear to show activity against SARS-CoV-2 infection, released data remain insufficient (non-peer-reviewed) and often uncontrolled at this time. In a randomized double blind placebo controlled trial from China published in The Lancet[8] researchers studied 237 adult patients with severe COVID-19, giving the drug to 158 and comparing their progress with the remaining 79. Patients were hospitalized with confirmed COVID-19 pneumonia and hypoxia and randomized within 12 days of admission. The primary endpoints were death or discharge at day 28. Remdesivir was not associated with statistically significant clinical benefits, although reduction in number of days to clinical improvement was observed in those treated earlier in their illness. The ACTT Trial[9] is an NIH double blind, randomized, placebo based trial. It has enrolled 1,063 patients at 68 sites in the United States, Europe, and Asia. Patients have confirmed COVID-19 infection with pneumonia and hypoxia. An independent data and safety monitoring board (DSMB) overseeing the trial met on April 27 to review data and shared their interim analysis with the study team. Preliminary results indicate that in the patients who received remdesivir, the median time to recovery was 11 days compared with 15 days for those who received placebo. Recovery in this study was defined as being well enough for hospital discharge or returning to normal activity level. Results also suggested the possibility of a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ($p = 0.059$). This is of borderline statistical significance and therefore the final trail results will be needed to evaluate whether remdesivir will have a mortality benefit. Lastly, in an uncontrolled cohort of 61 United States patients hospitalized for severe COVID-19 and who were treated with compassionate-use IV remdesivir, modest clinical improvement in oxygenation was observed in 36 of 53 patients (68%). Based on this data, remdesivir, although appearing to show significant activity against SARS-CoV-2 infection, may not alter the disease trajectory in severely infected patients. This is predominantly related to that fact that in most acute viral diseases, COVID-19 included, viremia peaks in the first week after infection and patients usually develop a primary immune response by day 10 to 14, which is followed by virus clearance. Most patients have been enrolled into the ACTT trial after day 7 of symptom onset. After this time point, if a patient's status deteriorates, it is usually the result of inflammatory or hyperimmune attacks (cytokine storm) rather than direct viral-induced tissue damage. If the ACTT trial confirms a clinical benefit to remdesivir, the next step will likely be a randomized trial of treatment beginning earlier in the disease trajectory.

Tracking population movement to predict flares of COVID-19 infection[10]

A paper recently published in Nature highlighted the very close relationship between population movements between Wuhan and other parts of China with the future pattern of novel coronavirus infections across that country. Using mobile phone positional data, researchers studied the actual movements of over 11 million observable individuals spending at least two hours within Wuhan, China, during the days of January 1 to 24, 2020 and overlaid these movement patterns against observed cases of COVID-19 through February 19, 2020. This created a population-flow-based "risk source" model that significantly outperformed traditional assumption-based epidemiological models in predicting future case counts. Interestingly, the predictive superiority of the population flow model increased over time, suggesting that it was better at incorporating dynamic changes in migration patterns occurring in response to the epidemic itself.

This research implies that similar collection of near-real-time movement data from cell phones in the United States could be a valuable tool in predicting and blunting future COVID-19 disease resurgence. Because our ability to accurately assess local disease prevalence will always be delayed by the incubation period and length of time for lab results to be obtained, outflow data tracking the movement of individuals from high prevalence locales could provide a high fidelity early-warning system. This study also highlights the potential dangers of resuming widespread business and leisure travel while low-level disease transmission persists. Transportation hubs and traditional vacation locales, including amusement parks, seaside towns, and national parks are likely to become transmission hotspots where people may become infected and then bring those infections back home with them.

COVID toe[11]

There is increased recognition of a specific dermatologic syndrome in younger patients with COVID-19 infection. These to date have been case reports involving up to 6 cases, or registries documenting scattered involvement in high prevalence areas. Thus, the incidence of this is unknown. Patients are usually aged 10-40, and often have the dermatologic symptoms as the sole manifestation of COVID-19 infection, or associated with mild fever and cough. Typically, the respiratory symptoms if present, are resolving or resolved at dermatological presentation. Not all of these patients have had confirmed testing, but the syndrome has peaked in parallel with the peak of documented cases in high prevalence areas in both Spain and France. The presentation is one of initial reddish papular lesions on the toes, heels, and less commonly the fingers. They resemble chilblains, painful inflammation of the small blood vessels of the skin. After a week or so they become flat and purpuric, and then slowly resolve. The lesions are mildly symptomatic with burning, itching or pain. One case report documented a lymphocytic vasculitis on skin biopsy. There are also cases of what appear to be microthrombi in the toes in more severe cases of COVID-19 infection. It is not known whether these cases are more severe presentations of the above, or related to the known hypercoagulability of more severe COVID-19 infection. Attention should be drawn to these dermatological manifestations as other symptoms may be minimal or absent in children and adolescents.

Serological analyses of patients with COVID-19, individuals with mild viral symptoms, and asymptomatic blood donors using novel assays[12]

For diagnostic purposes, serologic testing can complement SARS-CoV-2 detection by RT-PCR. At the population level, accurate serologic testing will be needed to identify who has been infected and to monitor regional transmission of COVID-19. Researchers from France recently developed four serological assays to detect antibodies to SARS-CoV-2. Target antigens varied for each assay:

- Two ELISA tests were developed using the full-length nucleoprotein or the extracellular trimeric spike protein as antigens, called the ELISA N and ELISA tri-S assays, respectively.
- The third assay, called S-Flow, detected antibodies binding to all domains and conformations of the spike protein expressed at the cell surface.
- The fourth assay, called LIPS (luciferase immunoprecipitation assay), targeted different domains of the spike and nucleoprotein.

The performance of each assay was evaluated by testing blood samples from different cohorts.

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Hospitalized patients with COVID-19: Among 51 hospitalized patients (161 blood samples), the percent of positive samples varied across assays from 65% to 72%. Although all hospitalized patients had laboratory-confirmed COVID-19, some samples were negative because they were collected prior to seroconversion. To characterize the time to seroconversion, samples were analyzed from 5 patients with known dates of symptom onset and ≥6 samples collected over time. In this cohort, seroconversion occurred between 5–10 days from symptom onset.

Pauci-symptomatic patients: 209 blood samples were obtained from individuals who participated in an epidemiologic tracing study after a school teacher tested positive for COVID-19. Each individual had mild viral symptoms (fever, cough, or dyspnea). Positivity rates varied from 27% to 36% across assays. The authors assert that the larger variability in positive results compared to hospitalized patients likely reflects the lower viral loads generated by patients with milder symptoms. Since only about one-third of the individuals were positive, sampling may have been done prior to seroconversion for some, and others may have had viral symptoms that were not from COVID-19.

Blood donors: 200 blood samples were tested from individuals who donated blood during the study period (March 20 and 24), who were from two regions without clear virus transmission, and who self-identified as asymptomatic. ELISA-N and LIPS assays were negative for all donors. The S-Flow assay detected 6 positive samples. When combined with the ELISA tri-S assay, only 2 donors scored strongly positive. Thus, only about 1% of asymptomatic individuals were positive. The low positivity rate may also suggest a low rate of seroconversion or delayed seroconversion among individuals with asymptomatic infections. S-Flow and ELISA tri-S appeared to be more sensitive.

Pre-epidemic blood samples: Blood samples collected prior to the COVID-19 pandemic were also tested. All samples were consistently negative, underscoring that prior exposure to human seasonal coronaviruses associated with the "common cold" did not produce cross-reaction with the newly developed SARS-CoV-2 assays.

Lastly, neutralizing antibodies play a key role in preventing reinfections for many viral diseases. After comparing assay performances from different cohorts, virus neutralization assays were conducted. In 9 hospitalized patients, neutralizing antibodies were detectable by day 5, reached 50% by days 7–14, and reached 100% by days 14–21. Higher antibody titers were associated with greater neutralizing activity. Altogether, the multiple assays allowed for a broad evaluation of SARS-CoV-2 seroprevalence and antibody profiling in different populations. Sensitivities of the assays varied. Future studies are needed to optimize assay accuracy and cost. However, this is important data as it is one of the first studies to document antibodies that appear to neutralize SARS-CoV-2. As government restrictions ease and regional COVID-19 transmission rates wax and wane, accurate measures of virus prevalence rates, prior infection rates, and antibody profiles are tantamount in informing infection control measures.

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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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