The opinions of the summary authors in this publication are their own and not necessarily those of the American Heart Association.

Dear Reader,

Our plans for the 2nd edition of GPM Journal Bytes changed dramatically based on the occurrence of the COVID-19 pandemic. Our writing group felt it was important to present data that was relevant to the pandemic through the lens of genomic and precision medicine. In this edition you will find succinct summaries of pertinent studies that help explain the inter-individual variability in disease manifestation and outcomes observed with COVID-19 infections. We hope these "Journal Bytes" help serve our community during these difficult times not only in spreading knowledge about COVID-19 but also in spurring new research initiatives and advances.

With best wishes,

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Chair, GPM Professional/Public Education & Publications Committee

Does variability across HLA genes affect susceptibility to COVID-19 infection?

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Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A, Thompson RF. Human leukocyte antigen susceptibility map for SARS-CoV-2. J Virol. Published online April 17, 2020. DOI: 10.1128/JVI.00510-20. Epub ahead of print.

Human leukocyte antigen (HLA) alleles, critical components of the viral antigen presentation pathway, may affect susceptibility to SARS-CoV-2 infection and severity of illness. Nguyen et al. performed in-silico analysis to assess the binding affinity of N=32,257 viral peptides from the SARS-CoV-2 proteome to 145 different HLA-A, -B, and -C alleles. HLA-B*46:01 had the fewest predicted binding peptides for SARS-CoV-2, suggesting individuals with this allele may be particularly vulnerable to COVID-19 (as has previously been noted with SARS). To assess for potential cross-protective immunity conferred by prior exposure to other common human coronaviruses, the authors identified highly conserved linear epitopes from other coronavirus subgenera, and 44 SARS-CoV-2 amino acid sequences that they anticipated would generate at least one peptide present in another common human coronavirus. HLA-A*02:02, HLA-B*15:03, and HLA-C*12:03 alleles were the top presenters of these conserved peptides. However, 56 different HLA alleles (including HLA-B*46:01) demonstrated no appreciable binding affinity to any of the conserved SARS-CoV-2 peptides, suggesting an overall lack of potential for cross-protective immunity from other human coronaviruses. Importantly, there was no correlation between the HLA allele frequency in the global population and allelic capacity for SARS-CoV-2 antigen presentation.

Is there an explanation for the higher COVID-19 mortality rate observed in men as compared to women?

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Sama IE, Ravera A, Santema BT, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. Eur Heart J. 2020 May 14;41(19):1810-1817. doi: 10.1093/eurheartj/ehaa373. PMID: 32388565

Age adjusted mortality rate with infection by the SARS-CoV-2 virus that binds to the angiotensin-converting enzyme (ACE) 2 receptor appears to be higher in men than women. The study by Sama et al attempts to provide an explanation for this observation by measuring ACE2 plasma concentrations in 2 heart failure cohorts without COVID-19 disease and demonstrates that circulating ACE2 levels are higher in men as compared to women independent of other factors such as use of ACE inhibitors or angiotensin receptor blockers. Multivariable analysis demonstrated that other factors such as a history of coronary artery bypass surgery, atrial fibrillation and NYHA class 2/3 heart failure were also independent predictors of increased ACE2 levels. Although this study does not provide a direct link between severity of COVID-19 disease and ACE2 levels in the general population it does attempt to provide an explanation for the sex-related disparities observed in outcomes in addition to other explanations available in literature such as increased bi-allelic *TLR7* and *TLR8* gene expression observed in women based on their X chromosome location that plays an important role in antiviral immune response.

Is COVID-19 antibody testing accurate enough to inform clinical, or policy, decisions?

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Mathur G, Mathur S. Antibody Testing For Covid-19: Can It Be Used As A Screening Tool In Areas With Low Prevalence? *Am J Clin Pathol*. 2020 May15; doi: 10.1093/ajcp/aqaa082. PMID:32412044

Diamandis P, Prassas I, Diamandis EP. Antibody tests for COVID-19: drawing attention to the importance of analytical specificity. *Clin Chem Lab Med.* 2020 May 9; DOI:10.1515/cclm-2020-0554 PMID:32386187

Antibody testing to determine an individual's exposure to SARS-CoV-2, the virus that causes COVID-19, has been proposed as an essential component of the process for making clinical and policy decisions as social distancing measures are relaxed. To date, more than 10 tests have received FDA approval in the US, and more than 90 are seeking approval under emergency use authorization. However, Diamandis et al. and Mathur and Mathur explain that understanding how sensitivity, specificity and the prevalence of the disease in a particular population affect positive and negative predictive values is critically important to making decisions about the utility of these tests and provide illustrative examples (e.g. in a population with a ≤5% COVID-19 prevalence, the specificity of the test needs to be 100% for high positive predictive value (PPV); for a prevalence of 10%, 99% specificity; for a prevalence of 15%, 98% specificity). Specificities of the currently approved US tests are provided in Mathur and Mathur and the FDA (fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-test-performance) and range from 94% to 100%. The Foundation for Innovative New Diagnostics (FIND), a global non-profit organization, in conjunction with the World Health Organization, has created an open access database (https://www.finddx.org/covid-19/dx-data/) that reports performance data (provided by manufacturer or obtained from publicly available data) on internationally-available tests (the sensitivity of the 63 tests in the FIND database range from 36.4% to 100%). The Infectious Disease Society of America has also released a policy statement that proposes issues that should be addressed prior to utilizing COVID-19 antibody testing to inform clinical decisions (such as potential cross-reactivity with common cold coronaviruses, lack of titers in many tests and need for universal standards.) (https://www.idsociety.org/globalassets/idsa/public-health/covid-19/idsa-covid-19-antibody-testing-primer.pdf)

Repurposing drugs for COVID-19: hope or hype?

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Drug repurposing (redeployment of existing medicines that have already been tested safe in humans) is an important strategy to combat COVID19. Here are the results from recent trials of drugs being repurposed for use in the treatment of COVID19 infection. Anti-inflammatory therapies such as IL1 and IL6 blockade show some some promising results. While, data from large observational registries show no benefit of chloroquine or hydroxychlorine and even demonstrate harm with these therapies.

Drug (s)	Original indication	RCT	N	Endpoints	Main Results
Interferon beta-1b+ lopinavir-ritonavir+ ribavirin vs. lopinavir-ritonvir + ribavirin Hung IF, Lancet May 8, 2020	Multiple sclerosis	Y	127	Virus shedding, symptoms, length of stay	Combination of 3 drugs had shorter time to negative viral swab (7 days IQR [5-11]) vs 2 drugs (12 days [8-15]; HR 4.37 [95% CI 1.86-10.24], p=0.001)
Anakinra (IL-1 blockade) Cavalli G, Lancet Rheum, May 7, 2020	Arthritis	N	45	Inflammatory biomarkers	Anakinra reduced C-reactive protein and improved respiratory function. At 21 days survival was 90% in anakinra group vs. 56% control (p=0.009).
Tocilizumab (IL-6 blockade) Press release, April 27, 2020	Arthritis	Y	129	Need to ventilation or death at 14 days	Lower proportion with primary outcome in tocilizumab group.
Remdesivir Beigel J, NEJM May 22, 2020	Ebola/SARS	Y	1063	Time to recovery	Faster median time to recovery with redmesivir vs. placebo (11 vs. 15 days, p<0.001). Mortality rate 7.1% with remdesivir vs. 11.9% with placebo (HR 0.70, 95% CI 0.47-1.04).
Hydroxychloroquine ± Azithromycin Rosenberg E, JAMA May 11, 2020	Lupus Arthritis	N	1438	In hospital mortality	No difference in mortality between treated groups vs. no drug treatment. HC + AZ (HR 1.35 [95% CI, 0.76-2.40]) HC alone (HR 1.08 [95% CI, 0.63-1.85]) AZ alone (HR 0.56 [95% CI, 0.26-1.21])
Hydroxychloroquine Geleris J, NEJM, May 7, 2020	Lupus Arthritis	N	1446	Intubation or death	No difference in death or intubation vs. no drug treatment (HR 1.04, 95% CI, 0.82-1.32)
Lopinavir-ritonavir Cao B, NEJM 2020; 382: 1787-99.	HIV	Y	199	Discharge from hospital or clinical improvement	No difference in clinical improvement (HR 1.31; 95% CI 0.95-1.80) or mortality -5.8%; 95% CI -17.3 to 5.7) vs. standard care.

Does ACE genetic variation affect the prevalence of COVID-19 infection and mortality?

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Delanghe JR, Speeckaert MM, De Buyzere ML. The host's angiotensin-converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections. Clin Chim Acta 2020 Jun;505:192-193. DOI: 10.1016/j.cca.2020.03.031. PMID: 32220422. PMCID: PMC7102561.

The SARS-CoV-2 virus that causes COVID-19 enters target cells by binding to angiotensin-converting enzyme 2 (ACE2) on the cell surface. The *ACE* gene that encodes a related enzyme, angiotensin converting enzyme 1 (ACE1), has a common intronic deletion/insertion (D/I) polymorphism. The D allele in *ACE* is associated with decreased expression of ACE2. The prevalence of the D and I alleles varies geographically. By comparing data from 25 European and western Asian countries, the authors found that the prevalence of COVID-19 infections and mortality were inversely correlated with the prevalence of the *ACE* D allele. These intriguing data suggest that the *ACE* D allele is a genetic modifier of COVID-19, and may be protective by decreasing expression of ACE2.

Does blood type impact risk of COVID-19 infection?

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Li J, Wang X, Chen J, Cai Y, Deng A, Yang M. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. Br J Haematol. 2020 May 7; doi: 10.111/bjh/16797. Epub ahead of print.

The ABO blood groups of patients with SARS-CoV-2 infection from 3 hospitals in Wuhan, China, were compared to a healthy group of controls from Wuhan. The authors report the proportion of blood group A in patients infected with SARS-CoV-2 was significantly higher than that in healthy controls (38.0% vs 32.2%, $p < 0.001$), while the proportion of blood group O in patients with SARS-CoV-2 was significantly lower than that in healthy controls (25.7% vs 33.8%, $p < 0.001$). This difference remained significant after correcting for age and sex. Interestingly, when examining co-morbid conditions, they found that the proportion of hypertension (41.7% vs 32.2%, $p = 0.031$) and hepatitis (85.7% vs 32.2%, $p < 0.01$) in blood group A was much higher than that in the control group. The mechanism by which blood type may alter susceptibility to SARS-CoV-2 infection requires further investigation.

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