Dear Colleagues,

As the new Chair of the GPM Professional/Public Education & Publications Committee, I am extremely pleased to present our third edition of GPM Journal Bytes. As you know, GPM Journal Bytes is intended to summarize important and relevant papers from multiple journal sources in the realm of genomic and precision medicine from the past quarter and provide concise summaries. Given that COVID remains a significant global concern, the current issue covers both COVID-related and non-COVID-related publications.

Our desire is to help save you time and keep you well informed. We welcome any suggestions you may have to help us make Journal Bytes serve you better. If you have any suggestions, or questions, please do not hesitate to contact us. And please do not forget to follow the GPM Council on twitter @GenPrecisionMed.

Best wishes,
Sharon Cresci MD, FAHA, FACC, FASE
Chair, GPM Professional/Public Education & Publications Committee

Is there heritability of left ventricular ejection fraction in individuals without heart failure/cardiomyopathy?

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Left ventricular ejection fraction (LVEF) is known to be a heritable trait but only 6 loci associated with LVEF have been identified to date. This study performed genome wide association study (GWAS) on 22,155 adults of non-Hispanic White, Hispanic/Latino, Asian, or Black/African ethnicity from the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort and on 4,483
individuals of European ancestry from the UK Biobank (UKB) cohort. Meta-analysis of GERA and UKB identified 2 loci that met GWAS significance for association with LVEF (a novel locus in \textit{TMEM40}, the gene encoding transmembrane protein 40, and a previously reported locus in \textit{BAG3}, the gene encoding BCL2-associated athanogene 3) and replicated these loci in an independent cohort (Biobank Japan). The authors evaluated whether the variants were associated with any antecedent cardiac condition (heart failure/ cardiomyopathy, hypertension, myocardial infarction, atrial fibrillation, valvular disease, and/or revascularization procedures), and found that \textit{BAG3} rs17617337 was nominally associated with heart failure/cardiomyopathy and \textit{TMEM40} rs11719526 was not associated with any antecedent condition; if the number of antecedent cardiac condition was included as a co-variate, the association between the \textit{BAG3} variant and LVEF was slightly attenuated but remained significant and the association between the \textit{TMEM40} variant and LVEF was not affected. This study demonstrates that GWAS in large populations of diverse ethnic populations can identify novel determinants of cardiac function, even in individuals who do not have cardiomyopathy or heart failure.

\textbf{Do inborn errors in RNA sensing-type I interferon immunity pathways affect COVID-19 prognosis?}

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The anti-viral type I interferon (IFN) response seems to be critical for host immunity against SARS-CoV-2 and exogenous administration of IFN is currently examined as a therapeutic option in these patients. This study by Zhang et al. examined the genome of 659 patients with life-threatening COVID-19 pneumonia and 534 subjects with asymptomatic or benign infection for inborn errors in the TLR-3 and IRF-7-dependent type I IFN response (13 loci in total). The authors detected 118 variants in the examined loci among the severe COVID-19 cases, 24 of which (detected in 23 patients) were deleterious leading to loss of expression, loss of function or severely hypomorphic protein expression; in contrast, only 1 variant with predicted loss-of-function effect was detected among patients with mild/asymptomatic disease. The observed variants led to the downregulation of the affected molecules and/or dampened type I IFN response in patients’ cells, allowed higher rates of SARS-CoV-2 replication when the cells were stimulated in vitro, and resulted in no detectable serum IFN\textsubscript{α} (in all 10/23 patients carrying the examined deleterious alleles for whom serum samples were available for measurement). The authors conclude that genetic predisposition to a dampened TLR-3/IRF-7 mediated type I IFN response may predispose individuals to a more severe COVID-19 disease course.
**Does our Neanderthal DNA make us susceptible to severe COVID-19?**

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Data from the COVID-19 Host Genetics Initiative have identified a region of 49.4 thousand bases on chromosome 3 that confers an odds ratio for requiring hospitalization from COVID-19 of 1.6 (95% confidence interval 1.42-1.79). The authors of this paper determined that single nucleotide polymorphisms in this region were present in the genome of the *Vindija 33.19* Neanderthals, who lived approximately 50,000 years ago in southern Europe. Interbreeding with Neanderthals at that time appears to have introduced the risk haplotype into the modern human population. The Neanderthal haplotype appears in South Asia at a frequency of 30%, in Europe at 8%, among admixed Americans at 4%, in East Asia at very low frequencies, and in Africa at almost zero frequency. Thus, differences in the frequency of the Neanderthal haplotype may underlie differences in susceptibility to severe COVID-19 among populations.

**Should we be doing genetic testing prior to prescribing clopidogrel?**

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Based on data suggesting that individuals are at a higher risk for clopidogrel resistance and ischemic events, clopidogrel’s drug labeling information has a black box warning emphasizing the need to identify patients who have loss of function (LOF) *CYP2C19* alleles prior to clopidogrel treatment and suggesting consideration of alternative antiplatelet therapy. However, current guidelines do not support genetic testing in the absence of prospective evidence demonstrating that altering antiplatelet therapy will improve ischemic outcomes. TAILOR-PCI randomized 5,302 acute coronary syndrome and stable coronary artery disease patients who underwent percutaneous coronary intervention to either point of care genetic testing with genotype-guided antiplatelet therapy vs. conventional clopidogrel therapy and found that, of the 1,849 patients with *CYP2C19* LOF variants, 4.0% in the genotype-guided therapy group and 5.9% in the conventional therapy group developed ischemic complications at 12 months (34% reduction in events) which did not reach statistical significance (95% CI, 0.43-1.02; P = 0.06). A post-hoc analysis showed an almost 80% risk reduction at 3 months and a pre-specified analysis allowing for multiple events per patient.
demonstrated a statistically significant 40% reduction in ischemic events (P = 0.01) with genotype-guided therapy. The authors conclude that considering these results in combination with other studies, such as POPular Genetics, the totality of evidence points towards potential benefit of CYP2C19 genetic testing prior to prescribing P2Y12 inhibitor therapy.

Can polygenic background influence disease penetrance in rare monogenic variant carriers?

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The interaction between monogenic and polygenic risk is poorly understood and may have implications for disease penetrance and expression. Polygenic risk scores are increasingly being developed for conditions such as coronary artery disease and cancer syndromes but implementation into clinical care has been challenging. In this manuscript, authors studied over 80,000 individuals from UK Biobank and Color Genomics finding marked gradients in disease risk based on polygenic background in monogenic risk variant carriers for familial hypercholesterolemia, hereditary breast and ovarian cancer and Lynch syndrome. The probability of disease by age 75 years ranged from 17% to 78% for coronary artery disease, 13% to 76% for breast cancer, and 11% to 80% for colon cancer. These results underscore the important interplay between monogenic risk variants and polygenic background and have implications not only for disease expression, but also for potentially developing new therapeutic strategies.

Do cardiometabolic traits contribute to an increased severity of COVID-19?

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Several risk factors for increased severity of COVID-19 have been identified including cardiometabolic traits, however, it is difficult to infer causal effects in observational studies. To overcome the issue of confounding, this study employed Mendelian randomization (MR) using genetic proxies for body mass index (BMI), lifetime smoking score, low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (SBP) and type 2 diabetes mellitus (T2D) and examined
their association with sepsis and COVID-19 disease severity in the UK Biobank and a Norwegian population cohort (HUNT study). The MR analyses showed that higher genetically proxied BMI and lifetime smoking score were associated with increased risk of developing sepsis as well as increased risk of severe COVID-19 with respiratory failure and hospitalization with COVID-19. There was no association with genetically proxied LDL-C, SBP, or T2D with the risk of sepsis or severe COVID-19. This study was limited to populations of European ancestry and future studies in additional ethnic groups will be important.

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