Dear Colleagues,

We would like to welcome you to the inaugural issue of Genomic and Precision Medicine (GPM) Journal Bytes, a publication prepared for you by your colleagues from the American Heart Association Council on Genomic and Precision Medicine. We will review manuscripts from multiple journal sources and publish a concise summary of important and pertinent papers with a genomic and precision medicine theme on a quarterly basis.

The inaugural issue comprises of studies that we believe were important and published in 2019. Our hope is to save you time and keep you well informed. If you have any questions or suggestions, please do not hesitate in contacting us. And please do not forget to follow the GPM Council on twitter @GenPrecisionMed as we will use this platform to announce the quarterly release of new issues when available.

Best wishes,
Naveen Pereira MD, FACC, FRCPE, FAHA
Chair, GPM Professional/Public Education & Publications Committee

After PCI should ticagrelor for all or genotype-guided anti-platelet therapy be prescribed?
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Claassens DMF, Vos GJA, Bergmeijer TO, et al.
A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI

POPular Genetics (clinicaltrials.gov NCT01761786) was a non-inferiority trial that randomized 2,751 STEMI patients undergoing primary PCI to a genotype-guided arm in which CYP2C19 wild-type patients were assigned to receive clopidogrel and those with CYP2C19 loss of function alleles *2 and or *3 were assigned ticagrelor or prasugrel. In the other randomized arm, all patients were assigned to ticagrelor as standard treatment without genetic testing. The primary net clinical benefit end point of a composite of major adverse cardiovascular events and major bleeding at 1 year post PCI was 5.1% in the genotype-guided group and 5.9% in the standard ticagrelor assigned group. Due to higher risk of bleeding, the results suggest that a genotype-guided approach (in which most patients will receive clopidogrel - 61% in this study) would be preferred to prescribing ticagrelor for all patients undergoing PCI. The results of TAILOR-PCI (clinicaltrials.gov NCT01742117) a superiority trial which is evaluating whether genotype-guided selection of oral P2Y12 inhibitor therapy improves ischemic outcomes will be presented in March, 2020.
Three strikes and you’re out! A new paradigm for complex inherited cardiovascular disease.
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Gifford et al performed whole-exome sequencing on a nuclear family (both parents and 3 children) characterized by asymptomatic parents but severe clinical presentation and childhood-onset left ventricular noncompaction cardiomyopathy (LVNC) in all three offspring. Whole-exome sequencing, and subsequent informatic and cardiac expression analyses, identified inheritance of three missense single nucleotide variants in the offspring, two (MYH7 L387F and MKL2 Q670H) in the father (who had subtle echocardiographic evidence of LVNC) and one (NKX2-5 A119S) in the mother (who had no echocardiographic evidence of LVNC); further analysis of unaffected family members (with no echocardiographic evidence of LVNC) confirmed that MKL2 Q670H alone was not sufficient to cause LVNC and that MYH7 L387F was a de novo mutation. The authors evaluated the functional significance of all three mutations by generating mice harboring these mutations individually, in pairs, and all three together, and found that only the triple-compound heterozygous (i.e. MYH7 L387F/ MKL2Q670H/+ NKX2-5 A119S/+ ) mice recapitulated the LVNC phenotype. Human iPSC-derived cardiomyocytes from multiple family members further supported the hypothesis that the NKX2-5 variant was a genetic modifier. This study recognizes the contribution of genetic modifiers to variable penetrance of complex inherited cardiovascular disease, and illustrates methodology to test the clinical importance of variants of unknown significance.

Genetic risk for Chemotherapy-Induced Cardiomyopathy
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Garcia-Pava P, Kim Y, Restrepo-Cordo MA, et al. Genetic Variants Associated with Cancer Therapy-Induced Cardiomyopathy
Circulation. 2019; 140;31-41.

Garcia-Pava et al. performed next-generation sequencing of cardiomyopathy genes in 213 patients with cancer therapy-induced cardiomyopathy (CCM). The burden of rare variants in the CCM cohort was compared with the burden in a cohort of healthy volunteers (N=445), participants in the Cancer Genome Atlas (N=2,053), and an ancestry-matched reference population. Among 9 pre-specified, established dilated cardiomyopathy genes, titin-truncating variants (TTNtvS) occurred in 7.5% of CCM patients vs. 1.1% of participants in the Cancer Genome Atlas and 0.7% of healthy volunteers. CCM patients with TTNtvS also had more heart failure hospitalizations and atrial fibrillation and less myocardial recovery than those without TTNtvS. The authors then demonstrated in an experimental mouse model, that treatment with anthracyclines resulted in persistent LV systolic dysfunction in Ttntv/+ mice. This study highlights the importance of TTNtvS in the susceptibility to and prognosis in CCM and raises the question whether genetic testing should be incorporated, in addition to cardiac biomarkers, for identification of patients who could be at high risk for the development of CCM.
Can genes tell us who needs PCSK9 inhibitors?
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PCSK9 inhibitors are novel lipid-lowering agents that are highly effective but expensive and inconvenient to administer. Therefore, it would be useful to target these drugs to patients who are most likely to benefit. Polygenic risk scores (PRS) for coronary artery disease (CAD) were obtained in patients from the ODYSSEY OUTCOMES trial who were receiving statins following acute coronary syndrome (ACS) admissions and had been randomized to the PCSK9 inhibitor alirocumab or placebo. There was an absolute reduction of MACE (death from CAD, nonfatal myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization) by alirocumab in high versus low PRS groups of 6.0% and 1.5%, respectively, and relative risk reduction by alirocumab of 37% versus 13%. Thus, genetic risk profiling may facilitate a precision medicine approach to select patients in whom PCSK9 inhibitors will be most effective.

A new statin-like drug?
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Inhibition of the enzyme ATP citrate lyase, located upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) in the cholesterol biosynthesis pathway, lowers LDL cholesterol levels. However, it is unknown if therapeutically targeting this enzyme will reduce cardiovascular events to the same extent as seen with inhibiting HMGCR by statins. A Mendelian randomization analysis was performed in 654,783 participants comparing genetic scores composed of variants in the ACLY and HMGCR genes and their association with plasma lipid levels and the risk of cardiovascular events. Both the ACLY and HMGCR scores were associated with an equivalent reduction in LDL levels with a similar change in the lipid composition of plasma lipoproteins. For each 10 mg/dl reduction in LDL levels, the ACLY and HMGCR scores showed a similar degree of reduction in the risk of major cardiovascular events. Neither score was associated with an increased risk of cancer. This study provides validation for ATP citrate lyase as a potential therapeutic target.

Hereditary transthyretin amyloid cardiomyopathy (hATTR-CM) due to the TTR V122I variant is an autosomal dominant disorder than can lead to heart failure in elderly individuals of African ancestry. The rates of achieving a clinical diagnosis in carriers is unknown. This study is a cross-sectional analysis of carriers and noncarriers of TTR V122I aged 50 years of older enrolled in two academic biobanks (Penn Medicine and Mount Sinai, 2007 to 2018). TTR V122I was associated with higher rates of heart failure. Ten of 92 TTR V122I carriers with heart failure (11%) were diagnosed as having hATTR-CM; the median time from onset of symptoms to clinical diagnosis was 3 years. With newly FDA approved therapies for TTR amyloidosis, improved recognition of patients affected with this disease is needed.

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