After a decade of genome-wide association studies (GWASs), there are now thousands of common genetic variants associated with common clinical outcomes, subphenotypes, and human traits. As predicted from the common disease-common variant hypothesis, GWAS has established that each common genetic variant associated with a clinical outcome of interest confers only a small proportion of the overall risk attributable to genetics. From these findings, many studies have generated genetic risk scores, a summation across multiple loci, as an estimate of individual-level risk. The hope is that these scores can be used in clinical settings to target patients for prevention, intervention, and treatment strategies.

There are multiple approaches to calculating genetic risk scores. The most straightforward calculation is the summation of the number of risk alleles a participant or patient has for a particular clinical outcome of interest. A common variation of this approach includes weighting the risk alleles by expected impact or effect size based on the previous studies. The genetic risk score is an appealing summation of risk, but there are many caveats and nuances related to its calculation, including the availability and quality of source data for the variants used in calculating the score, their associated effect sizes used in weighting, and their general sensitivity and specificity in predicting individual-level risk.

With numerous established risk loci, coronary heart disease is an excellent example of how GWASs have transformed our understanding of the cause and development of common clinical outcomes such as cardiovascular disease. Despite this success, the translation of these genetic findings to clinical care remains a difficult challenge. Incorporating genetic risk factors into the existing clinical prediction models for other cardiovascular traits has shown lackluster results, often showing similar predictive capacity to models, including family history (though more recent studies have demonstrated the independent use of genetic variants). The potential clinical impact of such work is clear—providing that personalized risk assessments for coronary heart disease would aid clinical decision-making for the prescription of statins, strong dietary recommendations, and preventative screening and would truly usher in the era of precision medicine for treatment of the leading cause of death in the United States.

In this issue, Iribarren et al make steps toward this goal by estimating coronary heart disease risk, augmenting the existing Framingham Risk Score with multilocus genetic risk scores and assessing the improvement of this model compared with the Framingham Risk Score alone. The study was conducted in the GERA (Genetic Epidemiology Resource in Adult Health and Aging) cohort, a set of consented participants from Kaiser Permanente Northern California members. Although GERA is racially/ethnically diverse as part of the larger Research Program on Genes, Environment, and Health cohort, this study was limited to participants of European descent owing to the availability of published GWAS findings based on this group. Phenotype and exposure data were collected using a combination of electronic health record data (International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification) and survey data (self-reported current height and weight, medical history, health behaviors, and race/ethnicity). The outcomes of interest included incident coronary heart disease events (myocardial infarction, stable angina, unstable angina, coronary by-pass, or percutaneous intervention) or death caused by coronary heart disease. All participants were genotyped on the Affymetrix Axiom, an array designed for cohorts drawn from diverse groups residing in the United States and genetic data targeting European-descent populations were used to calculate the genetic risk score.

Four multilocus genetic risk scores were considered for this study consisting of 8, 12, 36, and 51 single-nucleotide polymorphisms. The first 3 risk scores were drawn from genome-wide association findings available in the National Human Genome Research Institute-European Bioinformatics Institute GWAS Catalog (as of 2010 for the first 2 risk scores and 2013 for the latter risk scores) for coronary artery disease independent of the classical risk factors total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, smoking status, and type 2 diabetes mellitus. The fourth risk score included genetic variants associated with coronary artery disease regardless of their association with the classical risk factors. In addition to published GWAS findings, the latter 3 risk scores also included 4 imputed variants representing the haplotype B of ALOX5AP, a haplotype previously associated with coronary heart disease in European- and Asian-descent populations. All risk scores were calculated as the sum of the number of risk alleles weighted by each variant’s effect size estimated in CARDIoGRAMplusC4D, a consortium...
meta-analysis of European- and Asian-descent coronary artery disease cases (n=63,746) and controls (n=130,681). From this work, Iribarren et al. show that the inclusion of genetic variants into the existing Framingham Risk Score improves the ability to predict cardiovascular disease. In clinical practice, family history is often an inexpensive and reliable surrogate for genetic risk; this result shows that directly estimating the genetic load for cardiovascular disease produces better predictions than family history alone. Iribarren et al.

Further show that the genetic component of their new composite risk reclassifies high-risk individuals (reducing risk for some and increasing risk for others). Perhaps most importantly, from a study-wide perspective, treating this new high-risk group with statins would have prevented more total occurrences than those identified as high risk from the Framingham Risk Score alone. Thus, the broad use of this composite risk score would not only provide better individual risk assessment but would improve the treatment and prevention of cardiovascular disease on a population level.

Although this result is encouraging, additional work is needed to fully operationalize this approach in clinical care. The genetic risk score depends on high-quality genotypes from several hundred variants, which is a much larger scale than traditional genetic tests ordered in a clinical setting. Further, it is unclear when to suggest a patient should receive such testing, or how its expense would be covered in clinical operations. Also, given the potential variability in statin compliance and response, this approach may need to be combined with genetic markers predicting adverse events or decreased efficacy in response to statin therapy.

Finally, as with most studies in translational genetics, this study was restricted to European-descent participants only. One could argue that Iribarren et al. could have expanded the study to include participants of non-European descent given the diversity of the GERA cohort. While this may have been technically possible, comparatively little GWAS data are available for non-European–descent populations, particularly for blacks and Hispanics. This persistent bias in genomic discovery efforts threatens to widen the health disparities chasm because genomic predictors are fine-tuned for one population but not tested or developed in others. The existence of GERA and the expected Precision Medicine Initiative Cohort Program, among other large ongoing or planned studies that focus on diverse populations, promises to provide the data necessary for precision medicine to be truly for All of Us.

Disclosures

None.

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