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EDITORIAL COMMENT

Polygenic Risk Scoring for Coronary Heart Disease

The First Risk Factor*

Pradeep Natarajan, MD, MMSc

Absolute risk assessment for coronary heart disease (CHD) based on a composite of risk factors is the foundation of contemporary CHD prevention (1). Risk scores serve: 1) to identify individuals at greater risk of CHD over a given time frame; and 2) to establish candidacy for pharmacological preventive strategies. In this issue of the *Journal*, Inouye et al. (2) describe a framework of using polygenic risk scoring to complement clinical risk scoring to identify both high- and low-risk individuals.

SEE PAGE 1883

A HISTORICAL PERSPECTIVE OF CHD RISK ASSESSMENT

Nearly 5 decades ago, the Inter-Society Commission for Heart Disease Resources recommended "that a strategy of primary prevention of premature atherosclerotic diseases be adopted as long-term national policy for the United States" (3). The resultant MRFIT (Multiple Risk Factor Intervention Trial) showed that individuals with a greater burden of cardiovascular risk factors derive a greater absolute benefit from strategies to lower CHD risk (4). Accordingly, the National Cholesterol Education Program's first Adult Treatment Panel (ATP-I) guidelines in 1988 recommended more intensive low-density lipoprotein (LDL) cholesterol lowering among individuals with multiple CHD risk factors (5).

In the 1990s, the Framingham risk score, incorporating multiple risk categories to predict the onset of CHD within 10 years, was incorporated into the ATP-III (6). Using largely the same risk categories, the Pooled Cohort Equations incorporated additional cohorts and non-European Americans to develop a 10-year risk estimator for atherosclerotic cardiovascular disease. The Pooled Cohort Equations was adopted by the 2013 American College of Cardiology/American Heart Association joint cholesterol guidelines and is widely used in practice (1).

However, among younger individuals, the ability to discriminate risk remains challenging, because age is the most important clinical determinant of 10-year risk (7). Thus, our current approach for primary prevention has unintentionally neglected a central goal from the 1970 Inter-Society Commission: "primary prevention of premature atherosclerotic disease" (3).

SETTING A BASELINE CHD RISK TRAJECTORY

Genetics provides the opportunity to quantify lifetime CHD risk, independent of age, and long before the onset of clinical CHD risk factors and their discriminative capabilities. Inouye et al. (2) now estimate lifetime risk trajectories on the basis of a polygenic risk score comprised of 1.7 million single nucleotide polymorphisms (SNPs).

Family history of cardiovascular disease has long been recognized as a risk factor for cardiovascular disease, but self-reported family history is a poor surrogate for CHD polygenic risk prediction (8). Prior quantitative assessments of CHD polygenic risk were based on an additive weighted score comprised of independent SNPs significantly associated with CHD ($p < 5 \times 10^{-8}$) (8–11). Simulation analyses recently suggested that liberalizing p value thresholds for SNP

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From the Cardiovascular Research Center and Center for Genomic Medicine, Massachusetts General Hospital, Boston, Massachusetts; Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, Massachusetts; and the Department of Medicine, Harvard Medical School, Boston, Massachusetts. Dr. Natarajan has reported that he has no relationships relevant to the contents of this paper to disclose.

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inclusion while accounting for reduced precision and genomic correlation may improve polygenic risk prediction performance (12).

Inouye et al. (2) describe several advances to improve upon prior polygenic risk scores. First, the authors leverage orthogonal discovery efforts from different genotyping platforms to maximize information gleaned from both genome-wide and targeted genetic discovery analyses in the construction of "metaGRS." The degree of correlation ($r = 0.11$ to 0.27 across the 3 scores) indicates that complementary information is incorporated. Further, effect estimate precision is improved where the data overlap. Second, metaGRS captures additional variation influencing CHD risk: the 1.7 million SNPs explain 26.8% of CHD heritability. This translates into both larger effect estimates and positive predictive values compared with scores of only genome-wide significant SNPs. Third, the authors leverage the UK Biobank, a population-based biobank of ~500,000 adults living in the United Kingdom, to evaluate metaGRS performance.

Another expanded polygenic risk score for CHD, comprised of 6.6 million SNPs, was recently described (13). This approach uses full results from genome-wide association analyses, but reweights variants based on correlation and strength of association. Correlation was determined based on an external reference of individuals of European ancestry, with additional tuning performed within the UK Biobank. Inouye et al. (2) use genomic correlation from within UK Biobank to exclude highly correlated variants. Because CHD heritability explained by individual SNPs when ranked by strength of association is severely right-skewed, whether these methodological differences will lead to measurably different performances requires further study.

Inouye et al. (2) show that a CHD polygenic risk score is not well captured by conventional clinical risk factors (unlike familial hypercholesterolemia [FH], a monogenic condition, and LDL cholesterol) and complements conventional risk factors to improve risk discrimination. However, cardiometabolic biomarkers, including plasma lipids, have not been released for the UK Biobank yet, and are thus not incorporated in the current analysis. Although this may moderate incremental risk discrimination, it has been proposed that prognosis as opposed to area-under-the-curve is more appropriate for polygenic risk score utility (14). Additionally, perhaps the framework should be flipped—perhaps we should be considering what the incremental value of acquired clinical risk factors are to polygenic risk. A polygenic risk score is stable from birth and is likely to be readily clinically available early in life in the not-to-distant future.

MODIFYING CHD RISK TRAJECTORY

Although a CHD polygenic risk score is defined at birth, predicted trajectories are altered based on diverse longitudinal exposures. Inouye et al. (2) demonstrate that the acquisition or absence of clinical risk factors substantially adjusts risk distributions. This is concordant with observations that the presence or absence of desirable health-related behaviors can modulate CHD risk independent of polygenic risk (9,15).

The promise of "precision prevention" depends, in part, on its ability to motivate health behavior change (16). In a study of 203 asymptomatic adults, CHD polygenic risk disclosure did not alter behaviors after 6 months (17). In another study of 94 asymptomatic adults referred to preventive cardiology, CHD polygenic risk disclosure was modestly associated with weight loss and increased physical activity (18). Genetics, including its motivating influences, is likely to play a modest role among largely unselected individuals. Nevertheless, the authors of the present study and others disclosed a 10-year composite CHD risk estimate using conventional clinical CHD risk factors and a CHD polygenic risk score to 7,328 participants of the Finnish GeneRISK study (19). Preliminary analyses indicate that, at 18 months, 17% of smokers quit smoking and 13.7% experienced sustained weight loss. Although inclusion of CHD polygenic risk scoring is likely to refine CHD risk estimation, to what degree specifically CHD polygenic risk disclosure played a role in these behaviors is currently unknown.

The influence of statins for primary prevention was previously evaluated in the setting of high CHD polygenic risk. Clinically-defined subgroups in statin clinical trials all demonstrate similar relative CHD risk reduction from statins (20). However, individuals at high CHD polygenic risk in 3 statin primary prevention trials were more likely to derive greater both absolute and relative clinical benefit from statins (10,11). Concordantly, Inouye et al. (2) show that the relative risk conferred from a CHD polygenic risk score is attenuated in the presence of lipid-lowering and/or antihypertensive therapy (2). Thus, although CHD polygenic risk can be useful in establishing statin eligibility on the basis of absolute risk, the greater relative risk reduction would translate to greater anticipated benefit in the setting of high CHD polygenic risk for a given absolute estimated CHD risk. For example, FH affects ~1 in 200 to 250 individuals, is associated with ~3.5-fold risk of CHD,