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The first risk factor: Polygenic risk scoring for coronary heart disease

Pradeep Natarajan, MD, MMSc[1,2,3]

[1]Cardiovascular Research Center and Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA 02114

[2]Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA 02142

[3]Department of Medicine, Harvard Medical School, Boston, MA 02115

Coronary heart disease (CHD) absolute risk assessment 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 pharmacologic preventive strategies. In this issue of the *Journal*, Inouye et al describe a framework of using polygenic risk scoring to complement clinical risk scoring to identify both high and low risk individuals (Inouye M et al. *J Am Coll Cardiol*. 2018).

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.”(2) The resultant Multiple Risk Factor Intervention Trial (MRFIT) showed that individuals with a greater burden of cardiovascular risk factors derive a greater absolute benefit from strategies to lower CHD risk (3). Accordingly, the National Cholesterol Education Program (NCEP)’s first Adult Treatment Panel (ATP-I) guidelines in 1988 recommended more intensive low-density lipoprotein cholesterol (LDL-C)-lowering among individuals with multiple CHD risk factors.(4)

In the 1990s, Framingham Risk Score (FRS), incorporating multiple risk categories to predict the onset of coronary heart disease (CHD) within 10-years, was incporated into ATP-III.(5) Using largely the same risk categories, the Pooled Cohort Equations (PCE) incorporated additional cohorts and non-European Americans to develop a 10-year risk estimator for atherosclerotic cardiovascular disease (ASCVD). PCE was adopted by the 2013 American College of Cardiology (ACC) / American Heart Association (AHA) joint cholesterol guidelines and is widely used in practice (1).

Correspondence: Pradeep Natarajan, MD MMSc, Massachusetts General Hospital, 185 Cambridge St, CPZN 3.184, Boston, MA 02114, Telephone: 617-724-3526, Fax: 617-726-2203, pnatarajan@mgh.harvard.edu.

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However, among younger individuals, ability to discriminate risk remains challenging since age is the most important clinical determinant of 10-year risk.(6) 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.”

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 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 is a poor surrogate for CHD polygenic risk prediction.(7) Prior quantitative assessments of CHD polygenic risk are based on an additive weighted score comprised of independent SNPs significantly associated with CHD ($P < 5\times10^{-8}$)(7–10). Simulation analyses previously suggested that liberalizing P value thresholds for SNP inclusion while accounting for reduced precision and genomic correlation may improve polygenic risk prediction performance (11).

Inouye et al describe several advances to improve 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=0.11–0.27 across the three 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 to 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 UK, to evaluate metaGRS performance.

Another expanded polygenic risk score, comprised of 6.6 million SNPs, for CHD was recently described.(12) This approach uses full results from genome-wide association analyses but re-weights 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 use genomic correlation from within UK Biobank to exclude highly correlated variants. Since 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 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-C), 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 thus not incorporated in the current analysis. While 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.(13) 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

While a CHD polygenic risk score is defined at birth, predicted trajectories are altered based on diverse longitudinal exposures. Inouye et al demonstrate that the acquisition or absence of clinical risk factors substantially adjusts the distribution. This is concordant with observations that the presence or absence of desirable health-related behaviors can modulate CHD risk independent of polygenic risk (8,14).

The promise of ‘precision prevention’ depends, in part, on its ability to motivate health behavior change.(15) In a study of 203 asymptomatic adults, CHD polygenic risk disclosure did not alter behaviors after 6 months.(16) In another study of 94 asymptomatic adults referred, CHD polygenic risk disclosure was modestly associated with weight loss and increased physical activity.(17) 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. (ESHG, June 2018, Milan, Italy. Abstract no C01.2) Preliminary analyses indicate that, at 18 months, 17% of smokers quit smoking and 13.7% experienced sustained weight loss. While inclusion of CHD polygenic risk scoring is likely to refine CHD risk, to what degree specifically knowing CHD polygenic risk 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.(18) However, individuals at high CHD polygenic risk in three statin primary prevention trials were more likely to derive both greater absolute and relative clinical benefit from statins (9,10). Concordantly, Inouye et al show that the relative risk conferred from a CHD polygenic risk score is attenuated in the presence of lipid-lowering and/or anti-hypertensive therapy. Thus, while 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 200–250 individuals, is associated with ~3.5-fold risk of CHD, and retrospective analyses suggest a greater relative benefit of statins (19). Initiation of high-intensity statins is recommended in the setting of FH.(20) Analogously, ~1 in 20 individuals (~10-fold more than FH) have a CHD polygenic risk conferring ~3.5-fold risk of CHD, and retrospective analyses suggest a greater relative benefit of statins (9,10,12,21).

Future opportunities

CHD polygenic risk prediction improvements for those of European ancestry may be asymptotic. Since polygenic risk scores are derived from large-scale genome-wide association analyses among individuals largely of European ancestry, they inherently perform less optimally in non-Europeans and are biased toward European admixture (22). Genetic analyses within non-European cohorts may improve risk prediction (23).

Current CHD polygenic risk scores do not incorporate the full spectrum of genetic variation known to influence CHD risk. For example, rare pathogenic variants in *LDLR*, *PCSK9*, and *APOB* resulting in FH are typically not captured on genotyping arrays, the platform used to compute CHD polygenic risk, and require sequencing. Whole genome sequencing is the only single platform that can fully catalogue genomic variation.

Whether high CHD polygenic risk should be homogeneously managed or otherwise requires further study. CHD genetic variants represent diverse known and unknown pathways. Many individuals are likely to have multiple pathways genetically altered, but a ‘palette’ model has also been proposed – one where there may be key pathophysiologic processes that might be preferentially targeted for prevention for some individuals (24).

In addition to clinical risk factors, non-invasive imaging or additional biomarkers may refine short-term risk (<10 years) when lifetime risk of CHD is high due to high CHD polygenic risk. CAC, for example, is strongly predictive of short-term CHD risk. However, while CHD polygenic risk is established at birth, the development of acquired clinical risk factors and manifestation of CAC occur later in life. High CHD polygenic risk may prompt earlier CAC assessment, but optimal timing requires further study.

Prospective randomized controlled trials are typically necessary to prompt guideline and management changes. As more individuals are undergoing genome-wide genotyping in research and direct-to-consumer settings, readily identifying a large cohort of asymptomatic individuals at heighted CHD polygenic risk will become increasingly feasible.

Conclusions

The originally proposed framework for primary prevention of CHD in the US was to identify and prevent premature CHD. However, our current framework insufficiently identifies those likely to sustain premature CHD. Inouye et al show that incorporation of CHD polygenic risk with clinical risk factors can improve risk prediction and may help with identifying individuals who are candidates for earlier preventive therapies. Additionally, this single genetic test (currently <$100), only needs to be performed once, and this framework can be applied to calculate polygenic risk for virtually any trait.

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