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EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (K. NASIR, SECTION EDITOR)

How Do We Incorporate Polygenic Risk Scores in Cardiovascular Disease Risk Assessment and Management?

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Abstract

Purpose of Review The potential of polygenic risk scores (PRS) to improve atherosclerotic cardiovascular disease (ASCVD) risk assessment and management has stoked significant interest in their incorporation into clinical management. The goal of this review is to apprise the readers of the latest developments and evidence of PRS readiness for clinical integration. We also discuss current limitations that must be addressed before PRS can be implemented into routine clinical practice.

Recent Findings PRS have been shown to improve risk stratification for ASCVD and to identify patients who may derive increased benefit from primary and secondary prevention. Risk captured by PRS appears largely independent of traditional risk factors and can be ascertained at birth, prior to the development of traditional clinical risk factors. Genetic risk is modifiable through lifestyle modifications and medications.

Summary PRS offers a valuable way to improve early identification of actionable CVD risk. However, further work is needed before PRS can be implemented clinically.

Keywords Atherosclerosis · Cardiovascular disease · Coronary artery disease · Polygenic risk scores · Pooled cohort equation · Lifestyle

Introduction

Risk estimation is a foundational element of preventive cardiology. Accurate assessment of individual risk for atherosclerotic cardiovascular disease (ASCVD) is essential for identifying those who stand to benefit most from lifestyle and pharmacologic therapies. However, current ASCVD risk models do not fully capture risk variables, leaving many patients in borderline risk categories that lack clear direction for management and counseling.

Recent studies on polygenic risk scores (PRS) suggest that the use of these models of genetic risk could improve ASCVD risk assessment and management [1•, 2•, 3, 4••]. However, the clinical utility of polygenic risk information is still controversial [5]. This review aims to apprise the readers of the latest developments and evidence of PRS readiness for clinical integration. We also discuss current limitations that must be addressed before PRS can be implemented clinically.

Assessment and Management of Atherosclerotic Cardiovascular Disease Risk

ASCVD is a major cause of morbidity and mortality in developed countries. According to a 2020 update from the American Heart Association, the age-adjusted prevalence of all types of heart disease in the USA is 10.6%, and heart disease remains the leading cause of death in the USA [6].

In the late 1940s, the Framingham Heart Study (FHS) was initiated to identify common factors or characteristics that contribute to ASCVD [7]. The preliminary results published in 1957 noted that ASCVD was more common among men,

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older adults, those who were overweight, and those with pronounced hypertension and/or hypercholesterolemia [8]. Advancements from the FHS and other epidemiologic studies have led to the modern-day pooled cohort equation (PCE), which is a validated estimator of an individual's 10-year risk for a first ASCVD event, accounting for well-established risk factors for ASCVD [9].

However, risk prediction models for ASCVD have room for improvement. One study demonstrated that the PCE substantially overestimated ASCVD risk in a contemporary and ethnically diverse population followed over a 5-year period [10], suggesting that additional diagnostic information (in addition to what is accounted for by traditional risk scores) may be necessary to gain a better understanding of one's actual risk for an ASCVD event.

Heritability of Atherosclerotic Cardiovascular Disease

Many genetic studies of ASCVD focus on coronary artery disease (CAD). Family and twin studies have estimated that the heritability of CAD ranges between 40 and 60% [11]. The Framingham Offspring Study demonstrated that after adjusting for traditional risk factors, a parental history of premature CAD was associated with 2-fold odds of incident cardiovascular disease, suggesting an independent heritable basis for cardiovascular disease [12].

Studies on the genetic determinants of ASCVD have elucidated distinct models of inheritance. In some disorders, risk follows a more classical, Mendelian inheritance pattern in which the disease presents at a younger age and often with a more severe clinical phenotype, as in familial hypercholesterolemia (FH). In FH, genetic risk for ASCVD is due to a rare mutation, or pathogenic variant, in a single gene. The most common pathogenic variants for FH occur in genes encoding the LDL receptor (*LDLR*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), and apolipoprotein B (*APOB*) [13].

Although the impact of monogenic risk for ASCVD is significant, for the majority of the population, inherited risk is due to the cumulative impact of many common genetic variants, known as single nucleotide polymorphisms (SNPs), which each has a relatively small effect size [14•]. The aggregate of disease-associated SNPs within an individual is often referred to as polygenic risk.

For a little more than a decade, genome-wide association studies (GWAS) have driven the discovery of many ASCVD-associated SNPs. Briefly, an ASCVD-specific GWAS compares the genetic information of individuals with ASCVD with that of ASCVD-free controls to determine if there are statistically significant differences in the SNPs in cases versus controls. GWAS require large data sets to maximize power and limit false discovery. Given that millions of SNPs are analyzed concurrently, necessary corrections made for multiple testing have established a standard *P*-value threshold of $< 5 \times 10^{-8}$ for genome-wide significance [15]. From the discovery of the first CAD-associated SNP (9p21) in 2007, 163 SNPs were found within a decade to be associated with CAD at a level of genome-wide significance [16, 17].

History of Development of Polygenic Risk Scores

PRS can be developed to model the combined effects that many common genetic variants, or SNPs, may have on an individual's risk for disease. The history of PRS development can be separated into four phases: (1) unweighted PRS; (2) weighted PRS; (3) weighted PRS with loosened threshold for genome-wide significance; and (4) weighted genome-wide PRS.

The earliest versions of PRS were unweighted, meaning that each genetic variant included in the score was assumed to have an equal effect size [18]. However, given that each risk variant tends to differ in its strength of association with ASCVD, the performance of these unweighted scores was understandably limited [18, 19].

The next iteration of PRS included the SNPs with GWAS-derived weighted associations with ASCVD. Ripatti et al. [20] developed one such PRS with 13 weighted SNPs and tested its performance in prospective cohorts from the Malmo Diet and Cancer Study (MDCS) and Finland Cardiovascular Risk Study (FINRISK). This 13-SNP PRS was strongly associated with incident CAD but did not improve risk classification beyond traditional risk factors or family history [20]. However, a later study in MDCS conducted by Tada et al. [21] found that a PRS with 50 SNPs (weighted, each having genome-wide significance) and traditional clinical risk factors could modestly improve model discrimination and reclassification. Of note, this 50-SNP PRS was also found to account for risk that was independent of self-reported family history of CAD [21].

The third phase in PRS development demonstrated a predictive benefit of lowering the threshold of genome-wide significance to include more SNPs within the genetic risk model and subsequently capture more CAD heritability. This lowering of thresholds was in part enabled by the use of computational methods such as clumping and thresholding, which optimize the number of SNPs included in the PRS while also keeping the false discovery rate low [22]. Abraham et al. [23] used these methods to develop a PRS comprised of 49,310 SNPs, which was then applied to multiple prospective cohorts within the FHS and FINRISK [23]. This PRS showed marked performance improvement over previous PRS (comprised purely of SNPs at genome-wide significance) and showed improved discriminative and predictive performance over

the clinical risk factors included in the Framingham risk score [23].

The fourth and current phase of PRS development is marked by the creation of genome-wide PRS. Through the use of software that can account for linkage disequilibrium, or nonrandom assortment of alleles, PRS can now be made to include millions of SNPs from all over the genome. Among these state-of-the-art genome-wide PRS, two studies provide useful landmarks for current CAD PRS performance.

The first of these landmark studies, conducted by Khera et al. [1•], was notable for its ability to classify those at extreme risk for CAD. Applied in the UK Biobank, this 6.6 million–SNP PRS showed that individuals in the top 1% of risk had 5-fold odds of developing CAD [1•]. This is in contrast to the 49,310-SNP PRS developed by Abraham et al., which classified those in the top 1% of polygenic risk as having 3-fold odds of developing CAD [23].

The second landmark study, by Inouye et al. [2•], generated a 1.7 million–SNP PRS that demonstrated further improvements in risk discrimination and prediction. When tested in the UK Biobank, this PRS outperformed all individual risk factors as measured by discriminative capacity (C-statistic). This study also confirmed the findings of previous studies that suggested that risk captured by these SNPs occurs independently from clinical risk factors. However, the most significant finding of this study was that the polygenic risk strata characterized distinct, age-independent risk trajectories, thus demonstrating the possibility of ascertaining lifetime CAD risk early in life, prior to the onset of clinical or even subclinical risk factors [2•].

Polygenic Risk Scores for Risk Assessment and Management of Atherosclerotic Cardiovascular Disease

At present, no official guidelines are established for the use of PRS in clinical decision-making. However, evidence suggests that PRS could soon be ready for clinical implementation, with certain applications having a much clearer path to implementation than others [24••]. In this section, we outline current evidence for such applications and discuss how a PRS could be used in ASCVD risk assessment and management.

A number of studies have suggested that a PRS could be implemented alongside established frameworks, such as the PCE. For example, a study by Hindy et al. [25] analyzed a genome-wide PRS alongside the PCE within both UK Biobank and MDCS and found that the PRS improved the stratification of patients at borderline to intermediate risk (with a 2- to 4-fold difference between PRS strata) [26•]. Given that the 2018 American Heart Association/American College of Cardiology guidelines support the use of risk-enhancing factors to help guide statin initiation [26•], it is reasonable to suggest that a high PRS could serve as a risk-enhancing factor. A recent study by Aragam et al. [4••] investigated the use of high CAD PRS as a risk-enhancing factor by analyzing a genome-wide CAD PRS across three health systems. The group found that an additional 4.1% of primary prevention patients may be recommended for statin therapy if high CAD PRS were classified as a risk-enhancing factor [4••]. Furthermore, Hindy et al. [25] showed that a genome-wide PRS could be used to further stratify risk trajectories within each of the four PCE risk categories. Within each risk category, individuals in the top 20% of PRS had a 2- to 4-fold increased risk for incident CAD compared with individuals in the bottom 20% of PRS [25]. Together, these suggest an opportunity to integrate genetic and clinical risk enhancers to improve the classification of disease risk trajectories and to aid in clinical decision-making for patients with borderline risk.

Despite this evidence, the clinical use of a PRS alongside the PCE at the current time is controversial, particularly when applied to middle-aged adults. For example, Mosley et al. [27] evaluated the performance of a model that combined a genome-wide PRS (6.6 million SNPs) with the PCE in the Multiethnic Study of Atherosclerosis (MESA) and Atherosclerosis and Risk in Communities (ARIC) cohorts. The study showed that the PRS did not significantly improve risk classification, model discrimination, or calibration. Of note, the PRS alone produced a similar C-statistic to the PCE alone in both MESA (PRS: 0.672 vs. PCE: 0.660) and ARIC (PRS: 0.669 vs. PCE: 0.701) [27]. Given the well-established performance of traditional risk factors in middle-aged adults, the PCE remains the basis for risk assessment in this population.

However, the PCE has been validated only for individuals aged 40 years and older. Because genetic risk is present at birth and remains constant throughout life, for younger individuals who have not yet developed clinical risk factors such as hypertension, elevated cholesterol, and low high-density lipoprotein cholesterol, which are highly influenced by lifestyle and included in the PCE, a PRS could aid in the risk prediction and enable earlier interventions directed at primary prevention [28]. Nevertheless, prospective studies are needed to evaluate the use of PRS in younger populations.

A number of studies have also shown that the genetic risk identified by a PRS can be attenuated with lifestyle modifications and that individuals with high genetic risk tend to have improved response to primary and secondary preventive therapies [2•, 3, 29–31]. Khera et al. [29] tested a 50-SNP PRS in three prospective cohorts—ARIC, the Women's Genome Health Study (WGHS), and MDCS—and in the cross-sectional BioImage study. The group found that genetic risk was uniformly attenuated by healthy lifestyle, defined as engaging in at least 3 of 4 healthy lifestyle behaviors: regular physical activity, healthy diet, no obesity, no smoking. In particular, individuals with high PRS and a favorable lifestyle

had similar disease risk to individuals with low PRS and an unfavorable lifestyle. For those within the highest quintile of genetic risk, adherence to a healthy lifestyle was associated with a 50% reduction in disease risk and significant reductions in coronary artery calcium [29]. This study therefore suggests that polygenic risk can be modified through nonpharmacological strategies, with marked benefit in individuals with the highest risk.

Studies have also shown that individuals with high PRS may derive greater benefit from statin therapy [2•]. In an analysis of two primary prevention trials, Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and Justification for the Use of Statins in Prevention (JUPITER), Mega et al. [30] found a graded increase in benefit from statin therapy as PRS increased from low to high, as quantified by greater absolute and relative risk reductions for individuals at highest risk [30]. Furthermore, a study-level meta-analysis of ASCOT, JUPITER, and the West of Scotland Coronary Prevention Study (WOSCOPS) found that statin therapy provided an absolute risk reduction of 3.6% in individuals with high polygenic risk versus 1.3% in all other subgroups and a corresponding relative risk reduction of 46% in the high–polygenic risk subgroup versus 26% in all other subgroups [32]. These findings suggest that a PRS may be helpful in joint decision-making on when to initiate statin therapy.

Improved response to pharmacotherapy in individuals with high polygenic risk has also been noted for secondary prevention. In an analysis of the Cholesterol and Recurrent Events (CARE) and Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI-22) secondary prevention trials, individuals at high polygenic risk had the greatest benefit from statin therapy, again showing graded reductions in absolute and relative risk as PRS increased from low to high risk [30]. Recently, post hoc analysis of two outcome trials, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome during Treatment with Alirocumab (ODYSSEY-OUTCOMES), found that patients with high PRS derived greater benefit from PCSK9 inhibitor therapy, with substantial mitigation of risk as measured by greater absolute and relative risk reductions [31]. Although further studies are needed to validate these findings, current evidence suggests that PRS could be used to identify patients who are more likely to benefit from more-intensive LDL-C reduction, including the addition of PCSK9 inhibitors in secondary prevention.

From a population health perspective, waiting until late in life for the development of clinical ASCVD or a very high 10-year risk score as estimated by the PCE, which is primarily driven by age, to guide the initiation of more intensive lifestyle therapy and medical therapy could be viewed as effort applied too little and too late. The ultimate goal of preventive cardiology should be to prevent not only recurrent events in individuals with clinical ASCVD but also the development of any symptomatic ASCVD by early interventions including lifestyle and simple inexpensive generic therapies to lower LDL-C and blood pressure. This approach may lead not only to fewer individuals with clinical events but also to healthier aging, as cognitive decline in the elderly is strongly associated with the risk factors of hypertension, high cholesterol, and diabetes in middle age. Current guidelines support the use of genetic information to enact early primary prevention strategies, for example, in individuals found to have pathogenic variants in genes known to cause FH [26•]. However, even though FH is the most common monogenic disorder (estimated to affect 1:250 people worldwide), this condition accounts for only a small fraction of individuals with ASCVD [33–36].

The relative prevalence and clinical significance of monogenic compared with polygenic risk were analyzed by Khera et al. [37•] with regard to early-onset myocardial infarction. Among patients with early myocardial infarction, 1.7% had a pathogenic variant known to cause FH, whereas 17.3% had a high PRS (top 5%). Furthermore, the odds of disease were nearly equivalent between the two groups, with a pathogenic FH variant conferring a 3.8-fold increased risk and a high CAD PRS conferring a 3.7-fold increased risk. Thus, individuals with high PRS had risk equivalent to monogenic disease, but high PRS accounted for nearly 10 times the number of early myocardial infarction cases [37•]. Of note, patients with an FH variant had marked elevations in LDL-C (mean 206 mg/dL), whereas those with high PRS did not (mean 132 mg/dL), further evidence that risk conferred by high PRS occurs largely independent of traditional risk factors. The findings from this study suggest that developing a screening and prevention framework for high polygenic risk (Fig. 1), in conjunction with population screening for FH, could lead to greater improvements in population-level prevention.

With the evidence that a PRS may prognosticate risk in the absence of demonstrable, subclinical disease, PRS could also be used to guide preventive strategies to determine which individuals should be screened for subclinical coronary or carotid atherosclerosis with noninvasive imaging tests. In the BioImage study, the 50-SNP PRS was associated with coronary artery calcium as well as all-cause mortality, even among patients without angiographic evidence of CAD [29]. Thus, a PRS could enable early, targeted, imaging-based assessment of individuals at high polygenic risk for ASCVD—a population for whom the presence of coronary artery calcium could further inform joint decision-making for the initiation of statin therapy.

Delivering on the promise of these applications requires significant additional work. Even if these scores were to be incorporated into practice guidelines, considerable research is needed to address the challenges of adoption and implemen-

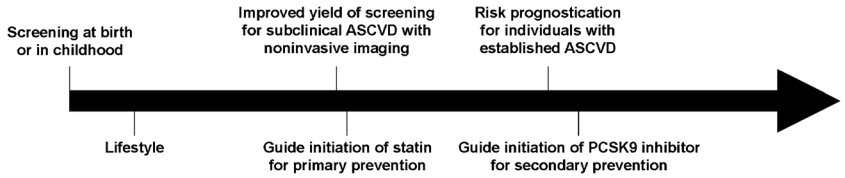

Fig. 1 Timeline for atherosclerotic cardiovascular disease prevention highlighting when polygenic risk scores have the potential to impact risk assessment and management. ASCVD, atherosclerotic cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9

tation of new practice guidelines [38]. Despite these challenges, actualizing the clinical utility of a PRS could provide a powerful new tool for identifying individuals earlier in life who may otherwise remain undetected by traditional risk assessment methods.

The Road to Clinical Implementation

For the clinical utility of genomic risk stratification to be realized fully, further work must be done to standardize PRS performance and to ensure that its implementation leads to equitable improvements in health outcomes.

At present, most GWAS have been conducted on individuals of European descent, leading to a strong bias toward this population [39]. Thus, without an ability to generalize reliably the performance of these scores to the population as a whole, premature implementation of PRS could further perpetuate existing health disparities present in different ethnic populations [40]. Further research in populations of diverse ancestry is necessary to improve the performance of PRS in multiethnic populations.

Furthermore, each step in the construction of the PRS itself needs to be standardized. Currently, there are numerous different PRS for ASCVD as well as diabetes and obesity, but none of them is standardized or accepted by any major cardiovascular guidelines. However, given the challenge of normalizing PRS performance across a population with variable genetic ancestry, it is not yet clear whether a single, standardized PRS for ASCVD could be applied across all clinical settings. Thus, work must still be done to determine whether one or many PRS will be required to generate comparable thresholds of risk across a variety of clinical settings [41].

Apart from predictive accuracy, the clinical utility of any prognostic risk tool is determined by its ability to reveal actionable risk. In the case of an ASCVD PRS, follow-through on the preventive strategies they identify will require individuals to make sustainable behavior changes. Studies to date on behavior change prompted by PRS disclosure have produced mixed results. The Myocardial Infarction Genes (MI-GENES) trial randomized 203 patients with intermediate polygenic risk for CAD into two groups. One group underwent risk counseling with clinical risk factors alone, while the other group underwent risk counseling with a combination of clinical and genetic risk factors. At the end of 6 months, diet and exercise patterns did not differ between the groups. However, the study did find that participants counseled with both clinical and genetic risk factors were more likely to be started on statin therapy, leading to lower LDL-C levels in this group [41]. Two additional studies on genetic risk disclosure showed that PRS results could be delivered in the outpatient setting, but neither study found improvements in lifestyle or adherence to preventive therapy [42, 43].

The challenge of motivating behavior change with information on ASCVD risk is not a new one, as similar difficulties have been described in studies on imaging-based risk assessments, such as carotid ultrasonography and coronary computed tomography [44–46]. Several studies have also found that being diagnosed or treated for hypertension, CAD, or chronic disease in general does not result in significant health behavior change [47, 48]. Thus, at present, little evidence suggests that simply communicating polygenic risk alone will result in positive health behavior changes.

Even so, the issue surrounding PRS and behavior modification should be reframed. The suggested value of a PRS lies in its ability to improve risk stratification, prognostication, and potential response to treatment—not in its ability to produce information that promotes health behavior change. Rather than being used to guide individuals, polygenic risk information may be better suited to guide healthcare systems in determining where behavioral intervention might produce the greatest return on investment [49]. Therefore, further research should be done to develop and evaluate effective methods for delivering ASCVD PRS information alongside established behavioral interventions.

Conclusions

Our collective understanding of the genetic architecture for ASCVD has grown substantially in recent years. Swift advancements in PRS development have given rise to an ability to chart lifetime risk for ASCVD and have markedly improved the ability to identify individuals likely to benefit the most from primary and secondary prevention strategies. However, before these scores can be widely deployed, work must be done to standardize the process of PRS development and to improve the performance of these scores in multiethnic

populations. Further research is also necessary to determine how ASCVD PRS disclosure can be integrated alongside effective health behavior interventions.

Compliance with Ethical Standards

Conflict of Interest Trevor Hadley and Ali M. Agha have nothing to disclose. Christie M. Ballantyne has received grant/research support through his institution from Abbott Diagnostic, Akcea, Amgen, Esperion, Novartis, Regeneron, and Roche Diagnostic and is a consultant for Abbott Diagnostics, Akcea, Althera, Amarin, Amgen, Arrowhead, AstraZeneca, Corvidia, Denka Seiken, Esperion, Gilead, Janssen, Matinas BioPharma Inc, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic and Sanofi-Synthelabo. He has received grant/research support through his institution from the National Institutes of Health, the American Heart Association, and the American Diabetes Association.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet 2018. 50:1219–24 **This study identified individuals with polygenic risk for coronary artery disease that was equivalent to individuals with familial hypercholesterolemia**.

2.• Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, et al. Genomic risk prediction of coronary artery disease in 480,000 adults: implications for primary prevention. J Am Coll Cardiol. 2018;72:1883–93 **This study showed that a genome-wide polygenic risk score could characterize marked differences in lifetime trajectories of coronary artery disease risk between strata**.

3. Damask A, Steg PG, Schwartz GG, Szarek M, Hagström E, Badimon L, et al. Patients with high genome-wide polygenic risk scores for coronary artery disease may receive greater clinical benefit from alirocumab treatment in the ODYSSEY OUTCOMES Trial. Circulation. 2020;141:624–36.

4.•• Aragam KG, Dobbyn A, Judy R, Chaffin M, Chaudhary K, Hindy G, et al. Limitations of contemporary guidelines for managing patients at high genetic risk of coronary artery disease. J Am Coll Cardiol. 2020;75:2769–80 **Original research demonstrating the added clinical utility of a coronary artery disease polygenic risk score over traditional risk factors**.

5. Khan SS, Cooper R, Greenland P. Do polygenic risk scores improve patient selection for prevention of coronary artery disease? JAMA. 2020;323:614–5.

6. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation. 2020;141:e139–596.

7. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Vol. 383. The Lancet. 2014;383:999–1008.

8. Dawber TR, Moore FE, Mann GV. Coronary heart disease in the Framingham study. Am J Public Health Nations Health. 1957;47(4 pt 2):4–24.

9. Muntner P, Colantonio LD, Cushman M, Goff DC, Howard G, Howard VJ, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA. 2014;311:1406–15.

10. Rana JS, Tabada GH, Solomon MD, Lo JC, Jaffe MG, Sung SH, et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. J Am Coll Cardiol. 2016;67:2118–30.

11. McPherson R, Tybjaerg-Hansen A. Genetics of coronary artery disease. Circ Res. 2016;118:564–78.

12. Lloyd-Jones DM, Nam BH, D'Agostino RB, Levy D, Murabito JM, Wang TJ, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. JAMA. 2004;291:2204–11.

13. Sharifi M, Futema M, Nair D, Humphries SE. Genetic architecture of familial hypercholesterolaemia. Curr Cardiol Rep. 2017;19:44.

14.• Musunuru K, Kathiresan S. Genetics of common, complex coronary artery disease. Cell. 2019;177:132–45 **Review of the genetic architecture of coronary artery disease**.

15. Dudbridge F, Gusnanto A. Estimation of significance thresholds for genomewide association scans. Genet Epidemiol. 2008;32:227–34.

16. Erdmann J, Kessler T, Munoz Venegas L, Schunkert H. A decade of genome-wide association studies for coronary artery disease: the challenges ahead. Cardiovasc Res. 2018;114:1241–57.

17. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science. 2007;316:1491–3.

18. Kathiresan S, Melander O, Anevski D, Guiducci C, Burtt NP, Roos C, et al. Polymorphisms associated with cholesterol and risk of cardiovascular events. N Engl J Med. 2008;358:1240–9.

19. Thanassoulis G, Peloso GM, Pencina MJ, Hoffmann U, Fox CS, Cupples LA, et al. A genetic risk score is associated with incident cardiovascular disease and coronary artery calcium the Framingham Heart Study. Circ Cardiovasc Genet. 2012;5:113–21.

20. Ripatti S, Tikkanen E, Orho-Melander M, Havulinna AS, Silander K, Sharma A, et al. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. Lancet. 2010;376:1393–400.

21. Tada H, Melander O, Louie JZ, Catanese JJ, Rowland CM, Devlin JJ, et al. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. Eur Heart J. 2016;37:561–7.

22. Privé F, Vilhjálmsson BJ, Aschard H, Blum MGB. Making the most of clumping and thresholding for polygenic scores. Am J Hum Genet. 2019;105:1213–21.

23. Abraham G, Havulinna AS, Bhalala OG, Byars SG, de Livera AM, Yetukuri L, et al. Genomic prediction of coronary heart disease. Eur Heart J. 2016;37:3267–78.

24.•• Aragam KG, Natarajan P. Polygenic scores to assess atherosclerotic cardiovascular disease risk: clinical perspectives and basic implications. Circ Res. 2020;126:1159–77 **Recent review of the genetic basis of atherosclerotic cardiovascular disease and the clinical utility of polygenic risk scores for coronary artery disease**.

25. Hindy G, Aragam K, Chaffin M, Orho-Melander M, Melander O, Khera AV, et al. Integration of a genome-wide polygenic score with ACC/ AHA pooled cohorts equation in prediction of coronary artery disease events in >285,000 participants [abstract]. Circulation. 2019;140:A16565.

26.• Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082–143 **2018 US cholesterol guidelines**.

27. Mosley JD, Gupta DK, Tan J, Yao J, Wells QS, Shaffer CM, et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. JAMA. 2020;323:627–35.

28. Natarajan P. Polygenic risk scoring for coronary heart disease: the first risk factor. J Am Coll Cardiol. 2018;72(16):1894–7.

29. Khera A. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med. 2016;375:2349–58.

30. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield MJ, Devlin JJ, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. Lancet. 2015;385:2264–71.

31. Marston NA, Kamanu FK, Nordio F, Gurmu Y, Roselli C, Sever PS, et al. Predicting benefit from evolocumab therapy in patients with atherosclerotic disease using a genetic risk score. Circulation. 2020;141:616–23.

32. Natarajan P, Young R, Stitziel NO, Padmanabhan S, Baber U, Mehran R, et al. Polygenic risk score identifies subgroup with higher burden of atherosclerosis and greater relative benefit from statin therapy in the primary prevention setting. Circulation. 2017;135:2091–101.

33. Hu P, Dharmayat KI, Stevens CAT, Sharabiani MTA, Jones RS, Watts GF, et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease. Circulation. 2020;141:1742–59.

34. Watts GF, Gidding S, Wierzbicki AS, Toth PP, Alonso R, Brown WV, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Int J Cardiol. 2014;171:309–25.

35. Sjouke B, Kusters DM, Kindt I, Besseling J, Defesche JC, Sijbrands EJG, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. Eur Heart J. 2015;36:560–5.

36. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Eur Heart J. 2013;34:3478–90.

37.• Khera A. Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with early-onset myocardial infarction. Circulation. 2019;139:1593–602 **This article showed that of those with early myocardial infarction, high polygenic risk identified 10 times more individuals than did monogenic risk**.

38. Chan WV, Pearson TA, Bennett GC, Cushman WC, Gaziano TA, Gorman PN, et al. ACC/AHA special report: clinical practice guideline implementation strategies: a summary of systematic reviews by the NHLBI Implementation Science Work Group: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation. 2017;135:e122–37.

39. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet. 2019;51:584–91.

40. Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. Hum Mol Genet. 2019;28:R133–42.

41. Kullo IJ, Jouni H, Austin EE, Brown SA, Kruisselbrink TM, Isseh IN, et al. Incorporating a genetic risk score into coronary heart disease risk estimates: effect on low-density lipoprotein cholesterol levels (the MI-GENES Clinical Trial). Circulation. 2016;133:1181–8.

42. Jouni H, Haddad RA, Marroush TS, Brown S-A, Kruisselbrink TM, Austin EE, et al. Shared decision-making following disclosure of coronary heart disease genetic risk: results from a randomized clinical trial. J Investig Med. 2017;65:681–8.

43. Knowles JW, Assimes TL, Kiernan M, Pavlovic A, Goldstein BA, Yank V, et al. Randomized trial of personal genomics for preventive cardiology. Circ Cardiovasc Genet. 2012;5:368–76.

44. Johnson HM, Einerson J, Korcarz CE, Aeschlimann SE, Stein JH. Long-term effects of carotid screening on patient outcomes and behaviors. Arch Intern Med. 2011;171:589–91.

45. O'Malley PG, Feuerstein IM, Taylor AJ. Impact of electron beam tomography, with or without case management, on motivation, behavioral change, and cardiovascular risk profile: a randomized controlled trial. JAMA. 2003;289:2215–23.

46. McEvoy JW, Blaha MJ, Nasir K, Yoon YE, Choi EK, Cho IS, et al. Impact of coronary computed tomographic angiography results on patient and physician behavior in a low-risk population. Arch Intern Med. 2011;171:1260–8.

47. Akbarpour S, Khalili D, Zeraati H, Mansournia MA, Ramezankhani A, Fotouhi A. Healthy lifestyle behaviors and control of hypertension among adult hypertensive patients. Sci Rep. 2018;8:8508.

48. Newson JT, Huguet N, Ramage-Morin PL, McCarthy MJ, Bernie J, Kaplan MS, et al. Health behaviour changes after diagnosis of chronic illness among Canadians aged 50 or older. Health Rep. 2012;23:49–53.

49. Masters R, Anwar E, Collins B, Cookson R, Capewell S. Return on investment of public health interventions: a systematic review. J Epidemiol Commun Health. 2017;71:827–34.