



Editorial

Precision Cardiology: From Risk Prediction to Risk Modification

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Cardiovascular prevention has been based on population-level risk equations for 50 years. The Framingham score and its iterations, such as the Pooled Cohort Equations (2013), were able to combine age, blood pressure, cholesterol, and smoking into a single likelihood of a future event. The benefit of this is that millions of lives were saved, but it is a method of managing risk that can be applied to a crowd and not a signature that belongs to one patient. “Precision cardiology” is an attempt to fill that gap: from predicting who will have a heart attack because they are like you, to understanding why you, in particular, might, and what can be done about it before it happens. The field is now clearly becoming divided into two active but distinct enterprises: sharper prediction and targeted modification, where the question is now: is the second catching up to the first?

Prediction has become genuinely multidimensional

The 2023 American Heart Association PREVENT equations mark the most significant recalibration of risk prediction in a decade. Unlike the Pooled Cohort Equations, PREVENT estimates 10- and 30-year risk for total cardiovascular disease, atherosclerotic events, and heart failure together, incorporates estimated glomerular filtration rate, and formally folds in the cardiovascular-kidney-metabolic (CKM) framework rather than treating diabetes, obesity, and kidney disease as afterthoughts.^{1,2} A genomic layer overlays this clinical layer. The small effects of thousands of common variants have been combined into a polygenic risk score (PRS) that now demonstrably has value to add to clinical risk scores such as coronary artery calcium scores; an analysis published in the Journal of the American Medical Association in 2023 revealed that combining the PRS with the calcium score reclassified risk more accurately than either alone.³ Newer analyses presented at the 2025 meeting of the American Heart Association (AHA) yield this benefit for PREVENT itself and, across ancestral groups, indicate that the genomic layer and the clinical layer are neither competing for the

same benefit nor redundant.⁴

This prompted the European Society of Cardiology to release its first clinical consensus statement on PRS in cardiovascular practice in 2025, which was a carefully worded, clear endorsement of genomic risk stratification as a complement rather than a substitute for traditional methods.⁵ Machine-learning techniques are also now being applied to further develop the construction of PRSs, making them more portable and noise-free, but systematic reviews suggest that most of this work is still in the proof-of-concept stage and requires bedside validation.⁶

Prediction without a force is an academic exercise

The usefulness of a more accurate risk estimate lies only in what a clinician can do based on that assessment. The most illustrative is the case of lipoproteins, specifically, lipoprotein (a) or Lp (a), a particle that is genetically determined, but largely lifestyle-resistant and now known to be an independent and causal contributor to both atherosclerotic disease and aortic stenosis. Lp (a) used to be in the unpleasant category of ‘risk factors we can measure but not treat’, until recently. This is quickly shifting. In phase 2 studies, antisense agents (pelacarsen) and small interfering RNA (siRNA) agents (olpasiran and lepodisiran) have been seen to reduce Lp (a) levels by 80-95%.^{7,8} The event-driven, phase 3 outcomes trials of Lp (a) HORIZON and OCEAN (a) were also extended into 2026, highlighting that pharmacologic risk modification still has to establish that it reduces events, rather than just a biomarker.^{9,10}

That is the true challenge for precision cardiology: Who benefits from a specific, frequently costly or invasive procedure enough that it is worth their while — by elevated Lp (a), by PRS, by coronary calcium, by stage of coronary disease? The cardiovascular and renal benefits of GLP-1 receptor agonists and also of SGLT2 inhibitors were originally seen in the context of glycemic control, and they now have independent protection in these two organs that align directly with the glucose-lipid milieu (CKM) that the



patient is experiencing – and thereby can be sequenced to the CKM the patient is having rather than just the type of their diagnosis.^{11,12}

Where does the model break down?

Three problems keep precision cardiology from being routine practice. First, calibration and equity: Most PRS were developed in European-ancestry populations, and scores are inconsistent in other populations; scores have also been found to be inconsistent in European-ancestry populations. Second, standardization: no standardized method is regulated which is used for the construction or validation of PRS, so two commercial PRS for the same disease can give different and meaningful opinions about who is a high-risk patient. At the same time, the evidence of downstream benefit is sparse, and last – and most essentially – the data is of poor quality. Nearly all of the studies referenced above show the benefits of discrimination or reclassification; a statistical property and not a randomized demonstration that shows the reduction of events if the additional information (genetic or otherwise) is incorporated into the clinical risk classification, compared with acting on clinical risk alone. In fact, the research into risk prediction has outstripped the research on the all-important risk modification question, namely: “What should patients do?”^{13,14}

What editorial priority follows from this?

But what should be measured during the next stage of precision cardiology is not the number of variants included in a score; it should be whether it will influence a treatment decision that has improved outcomes in a trial that was specifically designed to test that difference. In practice, this translates into three priorities: Integrating PRS and multimodal risk tools into pragmatic, outcome-driven trials in addition to reclassification studies; Designing diverse reference datasets that risk tools will not inadvertently expand risk inequalities, that is, to classify patients into risk groups for which no risk-specific action is currently taken; and Matching every new risk group with a treatment that is specifically designed for that stratum, not a reclassification study (as the Lp (a) risk stratification is now being done). The promise of precision cardiology has never been just to say a more precise probability of disease. This was to translate this probability into an action-oriented and proportionate intervention. That half of the promise – the prediction half – has been accomplished in a great deal of ways; the other half – the modification half – is where cardiovascular medicine will win or lose the next decade.

Authors' Contribution

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Competing Interests

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