Is Coronary Atherosclerosis One Disease or Many?

Setting Realistic Expectations for Precision Medicine

A ge-adjusted mortality from coronary artery disease (CAD) has decreased substantially in recent decades, in large part, related to a combination of lifestyle modifications, pharmacological therapies, and revascularization strategies. But do we need a new approach? The *All of Us* Research Program (a cohort study within the Precision Medicine Initiative) will begin enrollment of ≥1 million participants in 2017. This landmark resource will enable investigation into the substantial interindividual variation in physiology, risk of disease, and response to therapy.

Perhaps CAD patients, currently lumped together in the guidelines and minds of clinicians, actually have one of many disease subtypes. Each such subtype might lead to CAD via a distinct driving pathway and thus benefit from distinct therapeutic approaches. The ability to transform disease taxonomy in this fashion is an often-cited expectation of precision medicine.[1] Alternatively, the manifestation of CAD might reflect a quantitative blend of causal risk pathways in each individual (Figure). Precision medicine might enable identification of new risk pathways, each with broad relevance to the CAD population.

Human genetics studies of CAD provide an opportunity to explore the 2 hypotheses: distinct driver in each person versus quantitative blend in each person. Whether complex traits are inherited via: (1) rare variants of large effect or (2) an amalgamation of common variants, each with modest effect has served as longstanding fodder for cocktail-party debates (among geneticists) and rigorous investigation alike.

Recent large-scale genetic association studies have explored both common and rare variants as they relate to CAD. So what have we learned? First, genetic association studies have identified ≈60 variants robustly associated with CAD. The vast majority of these variants are common in the population.[2] Although typically associated with modest (eg, 5%–10%) increases in risk, common variants in aggregate explain a far greater proportion of CAD heritability than rare variants. Second, few (if any) examples of robust gene-gene or gene-environment interactions have been noted. Put another way, a given risk variant or environmental exposure (eg, smoking) tends to have similar relative impact on risk of CAD regardless of one's genetic profile. Third, both common and rare variants have highlighted the same pathways likely to be causal for human atherosclerosis: low-density lipoprotein cholesterol, triglyceride-rich lipoproteins, lipoprotein(a), blood pressure, inflammation, transendothelial migration, smooth muscle proliferation, and vascular tone. Fourth, the vast majority of cardiovascular therapeutics in use today have demonstrated benefit across subgroups. Although the subgroup analyses that accompany major trials warrant scrutiny, very few significant interactions have been noted.

Precision medicine will in fact identify a small subset of individuals in whom an identifiable driving pathway accounts for much of their risk of CAD. For these individuals, a therapeutic regimen that incorporates specific targeting of this pathway is likely to be of substantial benefit. However, in the vast majority of
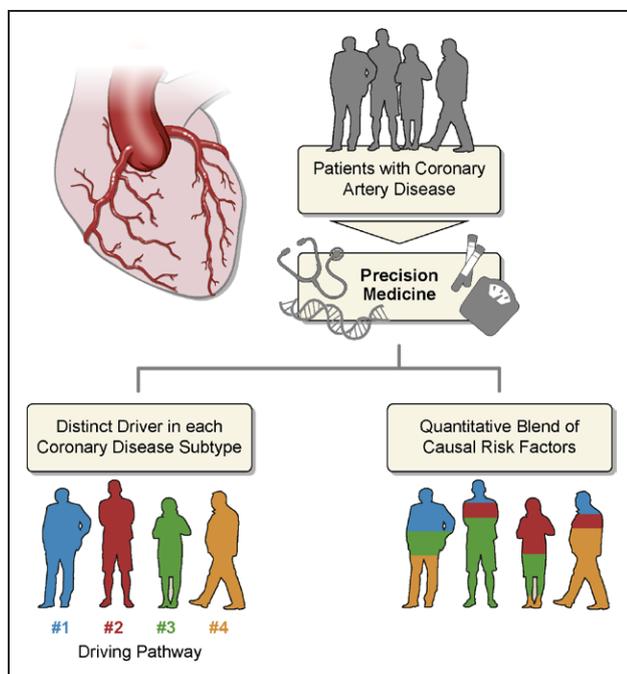
Amit V. Khera, MD
Sekar Kathiresan, MD

Figure. Coronary atherosclerosis: one disease or many?

One potential paradigm for precision medicine is that additional phenotyping might lead to the identification of a distinct driver (depicted by various colors in this schematic) in each individual. Alternatively, the manifestation of coronary artery disease in each individual may relate to a quantitative blend of such causal factors. Although not mutually exclusive, this dichotomy may help to frame expectations for the *All of Us* Research Program and other similar precision medicine biobanks.

CAD patients, it is a quantitative blend of causal processes that underlies disease. We thus believe that the principal value of genetics or other precision medicine efforts is not to subtype patients, but rather to highlight causal pathways that can be modulated for therapeutic gain.

Carl Müller first identified a familial pattern of xanthomata, hypercholesterolemia, and CAD in 1938.[3] We now recognize that familial hypercholesterolemia is attributable to defects in uptake of atherogenic low-density lipoprotein cholesterol particles by the low-density lipoprotein receptor. The systematic identification and treatment of individuals with familial hypercholesterolemia represent a significant opportunity to impact CAD risk for the estimated 1 in ≈250 with the condition. However, for the remaining 249 individuals, discoveries stemming from this rare Mendelian disorder that established low-density lipoprotein cholesterol as a causal etiology of human atherosclerosis have had even more impact. A 1980 publication first confirmed that a statin led to a ≈25% decrease in circulating cholesterol among 6 patients with heterozygous familial hypercholesterolemia (mean total cholesterol, 392 mg/dL).[4] Subsequent research confirming benefit of statin therapy across large

segments of the population has proven transformative for preventive cardiology.

Precision medicine will likely identify additional causal pathways that can be targeted in coming years. For example, a provocative study in a single family with multiple members experiencing a premature myocardial infarction noted rare defects in genes related to nitric oxide signaling.[5] These mutations were associated with diminished ability to generate nitric oxide from endothelial cells, increased platelet activation, and arterial thrombosis in mouse models. Just as with the initial studies of rare individuals with familial hypercholesterolemia mutations, biological insights into this pathway gained from individuals with rare, large-effect variants may facilitate drug development to promote nitric oxide signaling. Indeed, common variants in the nitric oxide signaling pathway genes are also associated with changes in CAD risk, suggesting that the pathway contributes as part of a quantitative blend of causal factors in the population at large.[3]

Beyond CAD, our oncology colleagues laid out a vision of identifying the specific driver mutations in each patient with cancer and targeting therapy accordingly over a decade ago: this notion has become reality for an important subset of patients. However, potentially even more influential was research demonstrating that tumor surveillance and immune system eradication was critical in preventing malignancy. This recognition of a key causal pathway led to a novel therapeutic approach, known as immunotherapy, that involves activation of the immune system to attack tumor cells. Because this approach is largely agnostic to the specific driver mutations of an individual cancer, immunotherapy is likely to have utility across a broad range of cancer subtypes.

In conclusion, is coronary atherosclerosis 1 disease or many? Although a small subset of the population may have a dominant driving pathway, we believe a quantitative blend of causal genetic and environmental factors underlies the majority of CAD cases. An expectation of a taxonomic revolution in complex disease derived from precision medicine efforts may lead to failure in the eyes of the public and funding agencies. Rather, we hope that large population-scale data resources will enable identification of the causal-risk pathways that contribute, albeit to varying degrees, to coronary atherosclerosis in *All of Us*.

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AFFILIATIONS

From Center for Genomic Medicine and Cardiology Division, Massachusetts General Hospital, Boston (A.V.K, S.K.); and the Program in Medical and Population Genetics, Broad Institute, Cambridge, MA (A.V.K, S.K.).

FOOTNOTES

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