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STATE-OF-THE-ART REVIEW

# Enabling Precision Cardiology Through Multiscale Biology and Systems Medicine

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## SUMMARY

The traditional paradigm of cardiovascular disease research derives insight from large-scale, broadly inclusive clinical studies of well-characterized pathologies. These insights are then put into practice according to standardized clinical guidelines. However, stagnation in the development of new cardiovascular therapies and variability in therapeutic response implies that this paradigm is insufficient for reducing the cardiovascular disease burden. In this state-of-the-art review, we examine 3 interconnected ideas we put forth as key concepts for enabling a transition to precision cardiology: 1) precision characterization of cardiovascular disease with machine learning methods; 2) the application of network models of disease to embrace disease complexity; and 3) using insights from the previous 2 ideas to enable pharmacology and polypharmacology systems for more precise drug-to-patient matching and patient-disease stratification. We conclude by exploring the challenges of applying a precision approach to cardiology, which arise from a deficit of the required resources and infrastructure, and emerging evidence for the clinical effectiveness of this nascent approach. (J Am Coll Cardiol Basic Trans Science 2017;2:311–27) © 2017 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The assumption of precision medicine is that insight into pathophysiological mechanisms of cardiovascular disease enables rational development of targeted treatments and procedures. Improved understanding of cardiovascular pathophysiologies comes at multiple scales. On the level of gross anatomy, understanding that occlusion of the coronary arteries typically leads to myocardial infarction or ventricular dysfunction led to the development of angiography and bypass surgery in the 1960s and 1970s, and later to percutaneous coronary intervention (1).

The arrival of molecular biology techniques in the 1970s and 1980s enabled the discovery of biological pathways such as the renin-angiotensin-aldosterone system. Such advances enabled the creation of drugs inhibiting specific targets such as angiotensin-converting enzyme (2). Angiotensin-converting enzyme inhibitors and other analogously designed drug classes, such as beta-blockers, 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, and glycoprotein IIb/IIIa inhibitors, have led to significant decreases in cardiovascular disease morbidity and mortality for millions of people around the world (3–5).

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**ABBREVIATIONS AND ACRONYMS**

**CAD** = coronary artery disease

**EHR** = electronic health record

**GWAS** = genome-wide association studies

**HF** = heart failure

Although targeting single molecules has worked for some cardiovascular diseases in the past, future success will require the adoption of new paradigms. Chronic cardiovascular disease encompasses a wide variety of pathological processes whose etiologies are genetic, environmental, and idiopathic. Even determining precise etiologies is often challenging. Although genome-wide association studies (GWAS) have revealed several highly significant loci (6–9) associated with cardiovascular disease (**Figure 1**), the overall contribution of these loci to heritability in complex disease is often <10% (10). This "missing heritability" poses a significant problem for drug discovery: it implies that the strategy of targeting genetic regions discovered via GWAS, phenome-wide association studies, or loss-of-function studies will not provide clear-cut improvements for managing complex cardiovascular diseases moving forward (11,12). The productivity of drug discovery pipelines has declined despite accumulating demand for new therapies (13–15). For example, highly targeted therapies such as the "-trapib" class of cholesterol esterase transfer protein inhibitors have repeatedly failed clinical trials (16–19).

In this state-of-the-art review, we identify 3 interconnected areas for new therapeutic opportunities in cardiovascular disease (20). First, we discuss the incorporation of precision medicine concepts into cardiology, or *precision cardiology*. We use the term *precision cardiology* to mean more accurate and refined characterization and stratification of disease states and individual patient pathologies using multiple molecular and clinical features (21). Precision characterization of cardiovascular disease consolidates heterogeneous sources of information into disease-related features. Until now, disease classification has relied upon experiential knowledge to decide a priori what information should be used to determine disease status. Instead, we propose to use multiscale data in combination with computational methods to better delineate boundaries between disease states, with the ultimate aim of choosing more precise therapies. Second, we generate and utilize disease networks to uncover and treat comorbidities associated with chronic cardiovascular diseases. Improved understanding of disease comorbidities will allow for new therapeutic opportunities. Third, we investigate the cardiovascular drug space in the frame of systems pharmacology, including drug repurposing and the identification of treatments that may act on multiple targets (polypharmacology). We conclude with a discussion on the potential role of precision cardiology in improving health care delivery through cost optimization, care coordination, and value-based standards of care.

## DEFINING PRECISION CARDIOLOGY

Despite enormous public interest and federal investment into precision medicine as epitomized by the recent establishment of the Precision Medicine Initiative (22–25), there are several competing definitions of precision medicine. The term is currently most often associated with the field of oncology, where rapid disease progression in cancer results from a series of somatic mutational events, which often clearly define a before- and after-disease state. This dichotomy provides a clear avenue to target treatments to an individual patient's mutational profile (26–29). The term is also used to define the application of genomic profiling and pharmacogenomics in a public health setting (30–33). Although genomic medicine (34,35) utilizes genetic information, we envision going further by incorporating information from the transcriptome, proteome, and metabolome with longitudinal health care data, such as disease diagnoses, procedures, medications, and environmental exposure data (36). We thus define precision cardiology as the application of multidimensional data to delineate subsets of the heterogeneous cardiovascular disease space. The ultimate aim of this approach is to enable patient stratification that can be used to better guide therapeutic interventions.

Many concepts from precision medicine in oncology are not directly applicable to cardiovascular diseases because there are substantial differences between heart disease and cancer. Somatic hypermutation is a central feature of cancer, but is not paramount in cardiology. Most cardiovascular diseases are chronic processes where the pathoetiology may begin decades before there are any symptomatic manifestations of the disease. Cardiovascular diseases are highly heterogeneous and present as comorbid or multimorbid with other conditions, whereas, for a given affected individual, cancer often presents as a more uniform pathological process (although an expressed malignancy in an individual can exhibit appreciable molecular and pathophysiological diversity due to clonal heterogeneity). Clinically, cardiology often uses broad, inclusive disease definitions that may conceal subtle disease variance. Symptoms are encountered late in disease progression. Finally, there is a strong temporal effect in cardiovascular disease—that is, the same disease encountered at different time points may require completely different interventions for prevention or treatment.