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 pathophysiology 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-

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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).

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.

**TRADITIONAL QUANTITATIVE APPROACHES ARE INADEQUATE FOR PRECISION CARDIOLOGY**

Several important factors drive the need to develop new quantitative approaches for precision cardiology. First, biological systems are inherently complex and display dynamic, emergent properties resulting from myriad potential interactions between individual molecules and coordinated pathways (37). In humans, vital functionality occurs at scales ranging from cellular genomics to gross anatomy, with numerous layers of molecular and cellular physiology in between. Second, there are challenges to interpreting data for several reasons. Data collected from patients during clinical encounters is often limited. When this information is entered into electronic health records (EHRs), limitations of this format can make later analysis more difficult. Because collecting data is
expensive and time-consuming in clinical settings, sample sizes are often small. Collectively, these challenges hinder our attempts to build comprehensive deterministic models of complex disease that could be used to better guide patient treatment.

Because of the issues with deterministic models, clinical researchers often utilize traditional statistical approaches such as logistic or Cox regression models. These techniques allow investigators to draw conclusions about associations between a limited number of predictor variables without complete characterization of the system.

However, tested hypotheses must be specified ahead of time, and these models do not easily fit data that may have underlying hidden structure (38). Instead, the implementation of more advanced computational and informatics approaches is an integral requirement for precision cardiology. Specifically, machine learning techniques can be used to model and explore data in an unsupervised fashion (Central Illustration).

Medicine lags behind other industries with regard to incorporating dynamic, longitudinal data into event detection and decision-making processes (39). For example, credit card companies collect large, longitudinal datasets containing customer information and individual transactions, but these datasets often do not include labels for whether particular transactions are fraudulent. Legitimate transactions generally far outnumber fraudulent transactions, and this unbalanced dependent variable problem has made the application of traditional statistical approaches unreliable. Instead, machine learning methods such as neural networks have been applied to solve this problem through separation of the entirety of the collected dataset into different strata representing different transaction classes. These classes are then tested for enrichment of different features, such as fraudulent transactions. This strategy has proven to be highly effective for fraud detection, and we propose the adoption of similar strategies to deal with medical data in cardiology (40). The practice of medicine and health care delivery is unique in that it must concern itself with patient safety and privacy concerns unparalleled in other industries. Nonetheless, we believe that medicine and, in particular, precision cardiology have much to gain by looking out into other industries and their use of data-driven methods. As an early example of the success of machine-learning in cardiology, data from devices such as the mobile electrocardiographic device Kardia (AliveCor Inc., San Francisco, California) have been successfully used in combination with machine learning to detect atrial fibrillation.

A great number of resources are available for incorporation into precision cardiology efforts. Clinical data traditionally collected from patients, such as vital signs, imaging results, laboratory tests, and patient histories, can be processed and incorporated into predictive models. Furthermore, machine learning methods have already been successfully applied to echocardiography results (41,42). We can also add patient descriptors, such as medications, diagnoses, procedures, and billing codes, to the set of clinical information. Other clinical data like medications can be linked to external adverse-event and drug-drug interaction databases. We also envision including information from emerging biosensors and consumer devices, such as smart watches or mobile health applications, into the data to be analyzed. Genomic information can be utilized in predictive models in the form of single nucleotide polymorphisms, copy number variants, and structural variants discovered from genome-wide association studies or other techniques. Associations from epigenetic, transcriptomic, and proteomic studies can also be added to represent genomic function. Metabolomics results (i.e., small molecules in fluids or tissues) present a tightly coupled representation of biological status related to clinical traits and may also be incorporated. The previous tools can then stratify phenotypes identified in phenotype-wide association studies. We collectively call this set of multiscale data multi-omics.

**ANALYZING CARDIOVASCULAR MULTISCALE DATA WITH MACHINE LEARNING METHODS**

In multi-omics studies, we do not know the exact mechanistic model that connects the different types of data. To address such uncertainties, statistical machine learning methods can be used to interrogate, model, and learn from complex multi-omics data.

The mathematical strategies underlying machine learning can be broadly defined as either supervised or unsupervised learning (Table 1). Supervised learning requires pre-defined labeling of the dataset (e.g., “cases” and “controls”). The labeled data is typically divided into training and testing datasets to reduce overfitting and produce better predictive models. Supervised learning algorithms (e.g., support vector machines, random forests, naive Bayes classifiers, as well as ensembles thereof) can be selected to perform a particular machine learning task depending on the nature of the data (continuous or categorical), sparseness or completeness of the data, or nature of the machine learning task (prediction, classification, and so on). Many classification and clustering
Multiple sources of heterogeneous data, including experimental evidence, bioinformatics databases, lifestyle measurements, electronic health records, environmental influences, and biobank findings, can be incorporated together using machine learning algorithms to identify causal disease networks, stratify patients, and ultimately predict more efficacious therapies.
problems in biology and medicine, including cardiovascular disease classification, precision phenotyping, and clinical diagnostic support systems, have leveraged machine learning methods (41,43,44).

Methods drawn from machine learning known collectively as “unsupervised learning” can be used to model and learn from multi-omics data. Unsupervised learning can broadly be described as an approach to machine learning to discover hidden structure in datasets without comparing the data to an external reference label, such as disease status, mortality rate, or other commonly studied dependent variables. This strategy is often used to reduce the dimension of noisy, highly multivariate datasets—essentially distilling complex sources of information into smaller representative datasets, which can then be more meaningfully used for downstream analysis. Many traditional approaches to unsupervised learning such as principal components analysis, singular value decomposition, and various methods of clustering remain robust and applicable despite their maturity. However, as a highly active area of interest in the computer science and bioinformatics communities, machine learning has been revolutionized in the context of medicine by a significant number of new, emerging techniques such as advanced algorithms for matrix factorization (45–47); topological data analysis (48–51); autoencoder artificial neural networks (52); and, in particular, deep learning, or artificial neural networks with multiple

| Type of Learning | Problem Tasks | Algorithms | Example Application in Cardiology | PMID |
|------------------|---------------|------------|------------------------------------|------|
| Supervised learning | Regression | Ordinary least squares regression | Many | |
| Classification | Logistic regression | Many | |
| Predictive modeling | Lasso regression | Sex-dependent risk factors for myocardial infarction | 25515680 |
| Survival analysis | Ridge regression | Discovery of biomarkers associated with CAD prognosis | 27224515 |
| Elastic net regression | Discovery of biomarkers associated with CAD prognosis | 27224515 |
| Naive Bayes | Classification of cardiovascular risk level | 27525161 |
| Support vector machines | Diagnosis of acute coronary syndrome | 26815338 |
| Information maximizing component analysis | Feature extraction of left ventricle shape changes following myocardial infarction | 26531126 |
| Bayesian networks | Meta-analysis of stroke prevention treatments; real-time prediction of cardiovascular events | 27570467; 26456181 |
| Decision trees | Estimating risk in congenital heart surgery | 26774238 |
| Random forests | Predictive modeling of chemoreflex sensitivity; predictive modeling of pediatric dilated cardiomyopathy from miRNAs | 27099934 |
| AdaBoost classifiers | Myocardial perfusion analysis from CT imaging | 26073787 |
| Neural networks | Length of hospital stay prediction; automated detection of stent failure; pharmacokinetics of losartan; prediction of heart failure outcomes | 27195660; 27036565; 26885213; 24387896 |
| Ensemble methods | All-cause mortality prediction | 27252451 |
| Unsupervised learning | Dimensionality reduction | Hierarchical clustering | Many | |
| Clustering | K means | Many | |
| Principal components | Self-organizing map neural network | Clustering ECG complexes | 10916254 |
| Linear discriminant analysis | Quantifying self-similarity of multimodal signals in the ICU; evaluation of atherosclerosis from multimodal imaging | 27454256; 25722204 |
| Topological data analysis | Pulmonary embolism diagnosis; few other examples | 26515513 |
| Deep learning | Ultrasound image processing; causal phenotype discovery | 21947526; 26958203 |

Table 1: Statistical Learning Approach to Precision Cardiology

Table of selected statistical learning approaches with previous example applications in cardiology.

CAD = coronary artery disease; CT = computed tomography; ECG = electrocardiogram; ICU = intensive care unit; miRNA = microribonucleic acid; PMID = PubMed identifier number.
layers of hidden neurons (53-62). To highlight 1 recent example of unsupervised learning, Li et al. (63) used topological data analysis to cluster patients with a diagnosis of type 2 diabetes mellitus into 3 separate subtypes of patients using data from a health system biobank, which included multiscale information from EHRs, clinical observations, and genetic data. In another example, deep learning-based denoising autoencoders were used successfully to build new aggregates of breast cancer gene expression data, which could then be used to predict mortality better than previous methods (52). Deep learning is perhaps the area of machine learning that has made the most rapid advance in recent years: in situations with large enough available datasets, deep learning has been demonstrated to produce best-of-class results and has thus been widely applied in areas such as drug discovery (58,59) and digital pathology (54,55). Briefly, deep learning strategies employ many layers of stacked models to represent data in hierarchies of concepts. Each layer is comprised of many different models, which interpret data provided to them and then pass their results to another higher-level model. This process is repeated until output results are obtained from the top-level model. In a recent study, Miotto et al. (36) demonstrated the promise of deep learning by applying the technique to model sparse, repetitive, and layered data found in the EHR to classify patient disease status in an unsupervised fashion. They termed this concept “deep patient” (36).

Accurate determination of a patient’s disease phenotypes can be a difficult problem. EHRs were established primarily to support health care provision and billing, and not for research. Moreover, different physicians, health systems, and scientists may use different criteria to diagnose a particular disease (64). These factors may lead to different conclusions and study results if not accounted for. The desire to consistently assign case and control status from EHRs has led to the development of standardized algorithms such as those from the eMERGE consortium (65,66). These electronic phenotyping algorithms serve to standardize patient populations across studies. Many such algorithms are deposited in the Phenotype KnowledgeBase (PheKB) (67), a centralized repository of validated E-phenotyping algorithms for high-quality phenotyping using EHR data (68). For each disease algorithm, case and control cohorts are defined using standardized criteria that can be consistently applied across different settings. However, due to the rigorous nature of these algorithms, only a limited amount has been developed to date. These algorithmic disease classification practices have an important role in building a foundation for more precise approaches. However, it is important to note that “E-phenotyping” approaches such as those by the eMERGE consortium are not a precision approach by themselves; instead, they generally propose to define the entire complexity of disease processes into simple “present” or “absent” disease classifications.

In contrast to the algorithmic “E-phenotyping” approach described in the previous text, a differing approach called computational phenotyping has emerged (69). The goal of computational phenotyping is to embrace the complexity inherent in disease mechanisms through machine learning approaches to define accurate phenotypes. Often, the goal is to use these phenotypes to model future responses in a dynamic fashion. For example, 1 group of investigators sought to discover new genetic diseases in patients with suspected genetic diseases. The investigators combined genetic sequencing with clinical trait data to build predictive scoring models for different putative mutations. They found that their model could correctly predict the genetic etiology for 28% of new cases for which there existed no previous diagnosis (70). In another example, the investigators developed a new machine-learning technique to predict antibiotic resistance phenotypes in a variety of bacterial species (71). Here, we envision a particular type of computational phenotyping that we call precision subtyping, which may use insights from both E-phenotyping (to establish baseline monolithic disease case-control cohorts) as well as from computational phenotyping (delineating new subsets of these cohorts).

CRITERIA FOR CARDIOVASCULAR DISEASES AMENABLE TO A PRECISION APPROACH

The diseases with the most potential to be treated in a more precise manner through multiscale approaches are those that meet several of the following criteria:

1. Diseases that are classified symptomatically or according to their clinical phenotype instead of according to pathoetiology. Such diseases may often arise from subtly distinct pathways that could benefit from data-driven differential treatment. Many cardiovascular diseases fit this paradigm. For example, essential hypertension is a disease defined purely phenotypically (systolic or diastolic hypertension). Using machine-learning strategies to stratify essential hypertension may allow for differential treatment on the basis of etiology. We believe there is a compelling need for more personalized approaches to hypertension
treatment, as current therapies are unsatisfactory. It is estimated that 44% of patients with essential hypertension were unable to achieve blood pressure control despite pharmacological therapy (72).

2. Diseases that are treated according to nonspecific guidelines or treatment algorithms established as the best practice by clinical trials that focus on the mean response to an intervention instead of examining variability in response (21). Precision approaches have an opportunity to capture variability and suggest possibilities for differential treatment. Again, many cardiovascular diseases fit this paradigm. Hypertension clinical trials, for example, generally examine outcome effects as the sample mean blood pressure is decreased. Stent clinical trials generally look at mean revascularization rates or other outcomes by device instead of allowing for more precise patient-to-device matching.

3. Diseases that are prominently characterized by biomarkers that do not reveal the underlying complexity of the disease. For example, atherosclerosis is strongly clinically associated with elevated low-density lipoprotein levels. However, the underlying biology is more complex, as suggested by the clinical failure of evacetrapib despite significant effects on low-density lipoprotein, and the accumulating evidence of the importance of the pleiotropic effects of statin therapy (73–77).

4. Diseases that manifest variably over an extended time frame, providing an axis upon which patients may be stratified and treated differentially. Coronary artery disease is a pertinent example: atherosclerosis is a progressive disease in which the first pathology typically emerges in one’s 20s, yet it takes decades to manifest symptomatically. Even when it does finally manifest, reasons for differential outcomes are complex and are not fully understood.

5. Diseases that are comorbid or multimorbid with other disease phenotypes. These diseases may in many cases have a specific molecular signature that could be corroborated with a pathophysiological mechanism. The majority of chronic cardiovascular pathologies have strong associations with comorbidities such as diabetes, obesity and metabolic syndrome, cancer (78), rheumatologic disease (79), as well as other cardiovascular diseases.

**EXAMPLES OF CARDIOVASCULAR DISEASES AMENABLE TO PRECISION SUBTYPING**

Profiling patient populations using multi-omics approaches could help us to perform precision phenotyping of several cardiovascular diseases (Figure 2). As noted by Antman and Loscalzo (21), 1 example of a cardiovascular phenotype amenable to more precise treatment is essential hypertension. Essential hypertension’s definition is based upon a single physiological finding; yet, it likely has a complex and varied pathoetiology that is not well accounted for in current clinical treatment guidelines (21,80). For example, a recent large meta-analysis of 18 studies containing 350,000 patients of varied ancestry with hypertension identified several rare single nucleotide variants with larger effect sizes than many common genetic variants associated with hypertension (81). The presence of substantial effect sizes with rare variants implies that there may be different or complementary molecular hypertension pathways. These different pathways may benefit from differential pharmacological treatment. Indeed, there are at least 10 different classes of drugs that can be used to treat hypertension (82); yet, standard guidelines and clinical trials generally emphasize a rote treatment algorithm in which drugs are used sequentially guided only by mean blood pressure measurements, and there are few attempts to tailor treatment to patients’ specific hypertension profiles (83,84).

Similarly, heart failure (HF) is another highly heterogeneous disease that results from complex interactions of dynamic physiological systems that are currently defined primarily symptomatically (85,86). For example, the New York Heart Association functional classes are completely symptomatic, although more recent classification systems now take into account pre-symptomatic and at-risk subjects (87). Even more objective measures such as left ventricular ejection fraction also only crudely predict the degree of disease, let alone underlying disturbances in physiology. The lack of proper measures that could be used for subset identification of HF patients has been implicated in the failure of recent HF trials (88,89). There have already been successful attempts at defining clusters of HF patients: for example, Ahmad et al. (90) used an unsupervised clustering approach to isolate 4 distinct clusters of HF patients: from clinical variables and biomarkers and found that the clusters were significantly associated with differential hospitalization and mortality risk. However, there remains an identified need for further efforts at HF patient stratification (91,92). To our knowledge, only a single paper published to date has attempted to apply deep learning methods to HF patients (57).

Finally, coronary artery disease (CAD) is the third example of cardiovascular disease amenable to a
more precision-oriented approach. CAD fits all of our criteria for precision medicine application: it develops over an extended period of decades, beginning with atherosclerosis and manifesting variably along a spectrum from asymptomatic to stable ischemic heart disease, acute coronary syndrome, and sudden cardiac death.

Furthermore, despite a plethora of imaging techniques and biomarkers, CAD is still primarily diagnosed and managed symptomatically (93). Recent advances in characterizing CAD gene networks (94,95) could be coupled with advanced imaging (96,97) and a wide variety of novel biomarkers (98–104) to stratify patients with this heterogeneous disease and make more informed treatment decisions.

DISEASE NETWORKS FOR PATIENT STRATIFICATION AND POPULATION HEALTH INTELLIGENCE

Network biology offers a powerful paradigm for representing and learning from complex biomedical data. In general, networks are defined as objects (called nodes or vertices) linked to each other by edges (called links or edges). Edges may be either directed or undirected. In biological applications, many different types of networks can be constructed on the basis of the availability of data types to define nodes (e.g., gene-gene network, gene-drug network, or gene-disease network). Edge relationships can be inferred based upon biological or clinical contexts (e.g., coexpression level, availability of drug-target information, and gene-disease linkage information) (Figure 3). The resulting networks can be analyzed using a set of algorithms to prioritize individual nodes, to prioritize network hubs, or to highlight subsets of nodes (subnetworks or cliques).

Network analysis metrics such as the clustering coefficient, centrality measures, and connectivity scores can then be used to characterize network properties and differences between disease states (105–109). Additionally, groups of highly related nodes can be tested for statistical enrichment of

In the precision approach to cardiology, multi-omic information is incorporated to identify subtle strata of patients which can be differentially treated within the existing therapeutic space. ACE = angiotensin-converting enzyme.
various properties, such as ontology or functional classification. To highlight a recent example of a biomedical network analysis, Glicksberg et al. (110) built a large-scale human disease network by compiling phenomic data from the EHR. The organized network used 1,988 disease conditions and 37,282 disease pairs from 1.02 million patients of 3 different ancestries: Caucasian, African American, and Asian.

**FIGURE 3** Comorbidity and Shared Genetic Architecture Between Hypertension and Coronary Artery Disease

(Top) Example of disease comorbidity networks for coronary artery disease (CAD) and hypertension (HTN), with comorbid diseases ascertained from Mount Sinai Hospital’s electronic health record data arranged around the central node. Distance from the central node is proportional to comorbidity odds ratio. We calculated comorbidity from ICD-9 codes using a logistic regression model controlling for age, sex, and self-reported ethnicity. Due to space limitations, we only show disease comorbidities with odds ratio ≥2. (Bottom) Networks of shared genetic architecture between CAD and HTN and other diseases, with shared genetic architecture defined as shared genome-wide association studies (GWAS) loci (gene level) between the 2 diseases. We compiled all data from GWASdb version 2 (August 2015) (159) and associated genes to a disease if they were GWAS threshold significant (p < 5 × 10^-8) and conferred an increased risk. We calculated shared genetic architecture using a 1-sided Fisher exact test. Distance from central node is proportional to odds ratio. DNA — deoxyribonucleic acid.
and Hispanic/Latino. Using this network, we identified several interesting pairwise disease comorbidities that may not be captured using traditional epidemiological studies. For example, we discovered 51 key “hub” diseases along with 2,158 significantly comorbid conditions for Caucasian patients, 3,265 for African-American patients, and 672 for Hispanic/Latino patients. By integrating network-level information with demographic information and genomic data, the sequelae of diseases can be used to identify the subsets of at-risk populations and stratify patients for optimized care delivery. In another recent example, we used a network approach to define cis and trans gene regulation of several hundred risk single nucleotide polymorphisms identified by GWAS for cardiometabolic diseases, providing strong evidence for extensive sharing of causal disease genes across tissues and different cardiometabolic diseases (95).

**DRUG REPOSITIONING AS AN AVENUE FOR DIRECTED INTERVENTIONS**

Drug repositioning is a drug-discovery strategy that relies on a priori knowledge to recommend an existing drug for a new indication based on evidence from clinical data (e.g., off-label prescriptions) or biological experiments (e.g., gene expression profiling after drug perturbations) (111,112). Briefly, drug repositioning (Figure 4) relies on the concept that biological processes are mediated by a finite set of genes or gene-products and several biological entities (e.g., genes, proteins, and transcripts) have pleiotropic effects and mediate similar functions. We outline a detailed overview of drug repositioning and various repositioning strategies in our recent review exploring experimental and computational approaches in the drug repositioning space (20,113). We recently developed a reference database for drug repositioning investigations using primary...
indications and secondary indications of rare, common, and chronic diseases (RepurposeDB) (114). By analyzing the RepurposeDB, we identified biological, chemical, and epidemiological factors driving successful drug repositioning. For example, 1 of the most prominent successes of drug repositioning is the example of beta-blockers for HF (115–117). Originally used as antihypertensive agents, they were once considered to be contraindicated in systolic HF, but are now the cornerstone of pharmacological management for this disease.

Another prominent example of repositioning is sildenafil. This compound was originally developed for hypertension, targeting the phosphodiesterase family of enzymes with the hope of augmenting atrial natriuretic peptide function by antagonizing breakdown of the second messenger molecule cyclic guanosine monophosphate. Pre-clinical trials showed that the compound’s actions lead to vasodilation, and the focus was then changed to angina. In clinical trials, it was noted that male patients reported the surprising side effect of penile erection after taking the drug. This observation allowed it to be eventually repositioned for erectile dysfunction. Later, it was observed that PDE-5 (a major target of sildenafil) was up-regulated in the lungs of patients with pulmonary hypertension (118). Sildenafil, as a known inhibitor of PDE-5, was then successfully repurposed for the indication of pulmonary hypertension (119,120). Similarly, several cardiovascular therapies have beneficial effects on other disease processes (e.g., aspirin for cancer) (121). Drugs like colchicine (122) that have systemic action are also particularly eligible for repurposing. It should be noted that no therapeutic interventions are devoid of side effects: onco-cardiology effects and the effect of chemotherapy are growing concerns of cancer patients in remission (123). Thus, building personalized prescription recommendation models to optimize therapeutic efficacy and limit side effects is a prominent goal of precision cardiology for both patient outcomes and cost-effectiveness. In addition to small molecules, recently, biological drugs (see the comprehensive list of small molecule and repurposed biological drugs compiled in RepurposeDB (124)) including monoclonal antibodies, peptide inhibitors, and microribonucleic acid-based therapeutics have shown potential for drug repositioning. Thus, exploring such emerging therapeutic interventions and their effect on cardiovascular disease could help accelerate repositioning discoveries in clinical trials (125–127).

**OPPORTUNITIES THROUGH POLYPHARMACOLOGY**

Polypharmacological therapeutic development refers to the goal of developing therapies targeting complex diseases like cardiovascular diseases and their known comorbidities, utilizing a multitarget approach (128–131). Briefly, polypharmacology aims to find a therapy or combination of therapies that would fit the patient more precisely than a generic therapy. For example, highly active antiretroviral therapy is a combination therapy used in human immunodeficiency virus treatment, sulfamethoxazole/trimethoprim is a combination drug targeting folate biosynthesis pathways in bacteria (132), and dalfopristin/quinupristin is another combination agent that targets the bacterial 50S ribosome (133). An extension of this approach called systems polypharmacology utilizes an entire network view rather than a single or a few targets, and is evolving as a new area of active research in pharmacology (134).

Although both multitarget therapeutics and systems pharmacology have led to several rational drug discovery candidates, their application in drug repositioning has thus far been limited. Performing drug repositioning studies on multitarget therapies could help to find new potential candidates for drug repositioning for cardiovascular disease.

**CHALLENGES IN INTEGRATING PRECISION CARDIOLOGY WITH OTHER MEDICAL SPECIALTIES**

The incidence rate of cardiovascular disease and the cost of management in the United States are increasing, which presents another potential application and opportunity for precision cardiology. For example, a recent estimate suggests that by 2030, 40.5% of patients will have at least 1 cardiovascular illness, which will raise the total cost of care to over $818 billion (135) worldwide. As cardiovascular-related conditions are often associated with lifestyle choices and have modifiable risk factors and well-characterized biological profiles, precision medicine approaches could help to reduce both the incidence rate and societal expense (12,136–138). However, unlike precision oncology, precision cardiology is missing several important building blocks to implement workflows in a clinical setting. For example, genomic profiling data are often siloed under individual investigator databases, and raw datasets available in resources like dbGAP are not
directly usable by cardiologists. The successful emergence of precision oncology can be attributed to the availability of several user-friendly bioinformatics resources, customized bioinformatics workflows, and unique datasets (e.g., genomics, transcriptomics, methylation, and proteomics) built as part of projects like The Cancer Genome Atlas. This raw, patient-level data is further used to create user-friendly applications like CBioPortal (139), which are fueling the genomic medicine revolution in oncology and could eventually lead to a standardized precision oncology practice (140,141). The recent announcement of the U.S. Cancer Moonshot initiative also offers continuous federal funding for innovative oncology projects that would further broaden the applications, reference databases, and resources required to implement precision oncology (142,143). Cardiology lacks both a centralized resource like The Cancer Genome Atlas as well as innovative funding programs that are a prerequisite for implementing precision practices. For example, building a Cardiovascular Disease Atlas by collecting longitudinal phenomic data integrated with multi-omics profiling using genomics, transcriptomics, proteomics, and metabolomics would be the foundation for enabling precision cardiology. A recent collaboration between the American Heart Association and Google proposed a moonshot grant, but unlike the 2020 Cancer Moonshot, the funding is restricted to a single project as part of a “1 team, 1 vision” approach (144). Furthermore, cardiologists and cardiovascular researchers should embrace practices including data sharing and other data commons strategies for faster knowledge distribution and dissemination of data for immediate replication, validation, reuse, and implementation into practice.

**PRECISION CARDIOLOGY:**
**MOVING FORWARD FROM COMPUTERS TO PATIENT COMMUNITIES**

Implementing precision cardiology in the clinical setting will require concerted efforts from undergraduate medical education, residency and fellowship training programs, medical school faculty, and practicing clinicians. Students must be trained in several interdisciplinary areas, including data science, mathematical modeling, systems biology, and bioinformatics, to become proficient practitioners (21,22,145,146). Cardiology clinicians and physician-scientists will need to collaborate with mathematicians, engineers, and bioinformatics scientists to build and apply complex models of disease. Furthermore, health care delivery experts and physician leadership will need to rapidly adopt new guidelines, personalized clinical workflows, and emerging regulatory frameworks. Patients and patient advocates will be a central component of implementing precision cardiology in the clinical setting (147,148). For example, communicating various aspects of precision medicine and including patients in clinical decisions using methods like shared-decision making is a vital step. Improvements in EHRs and clinical decision support tools will also be necessary. Design, development, and deployment of informatics applications and tools for visual analytics, predictive modeling, and risk analytics at the point-of-care are other key elements (149-151).

Integration with existing clinical infrastructure should promote cost-effectiveness as various longitudinal clinical data and some deep profiling data for large patient populations already exist (36,152,153). As the value of next-generation health care is a moving target and the current utility of precision medicine has been questioned, the success of precision cardiology will ultimately depend upon its effectiveness at reducing morbidity and mortality and increasing the quality of life for the cardiovascular patient population.

**PRECISION CARDIOLOGY: FUTURE OUTLOOK**

Physicians and scientists have a pressing need for a new paradigm to address deficiencies in the treatment of cardiovascular disease. The prevalence and incidence of cardiovascular diseases are increasing, and precision cardiology methods may offer a strategy to achieve improved outcomes while simultaneously decreasing health care expenditure (135). There are many early indications of the potential for precision cardiology through multi-omics methods, disease networks, and polypharmacology.

Application of these methods will become commonplace as data sources expand and it becomes easier to implement advanced algorithms. The current challenge with precision cardiology is determining how it can be most immediately translated into clinical practice to improve patient outcomes. The most ambitious precision cardiology plans require extensive data collection and analysis for which cost-effectiveness evidence does not currently exist. Such “translational-delays” from “bench-to-bedside” are not unexpected; consider the example of the implementation of pharmacogenetic testing for warfarin metabolism. Challenges such as the high cost of demonstrating utility in clinical trials and weaker intellectual property protections have delayed its uptake nationally (154). However, after years of doubt, recent studies have confirmed the
cost-effectiveness of this approach (155-158). It is likely that advances in precision cardiology will follow a similar path to clinical implementation. After demonstrating success through the integration of multidimensional and heterogeneous sources of data, there will be enough justification to collect, support, and maintain the next generation of clinical care and information gathering as well as to inform clinical trials for disease subtypes. As scientists and clinicians who care foremost about improving patient outcomes and delivering optimized patient care, enabling precision cardiology is an important step we can take.

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