Emerging Role of Precision Medicine in Cardiovascular Disease

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Abstract: **Precision medicine is an integrative approach to cardiovascular disease prevention and treatment that considers an individual's genetics, lifestyle, and exposures as determinants of their cardiovascular health and disease phenotypes. This focus overcomes the limitations of reductionism in medicine, which presumes that all patients with the same signs of disease share a common pathophenotype and, therefore, should be treated similarly. Precision medicine incorporates standard clinical and health record data with advanced panomics (ie, transcriptomics, epigenomics, proteomics, metabolomics, and microbiomics) for deep phenotyping. These phenotypic data can then be analyzed within the framework of molecular interaction (interactome) networks to uncover previously unrecognized disease phenotypes and relationships between diseases, and to select pharmacotherapeutics or identify potential protein–drug or drug–drug interactions. In this review, we discuss the current spectrum of cardiovascular health and disease, population averages and the response of extreme phenotypes to interventions, and population-based versus high-risk treatment strategies as a pretext to understanding a precision medicine approach to cardiovascular disease prevention and therapeutic interventions. We also consider the search for resilience and Mendelian disease genes and argue against the theory of a single causal gene/gene product as a mediator of the cardiovascular disease phenotype, as well as an Erlichian magic bullet to solve cardiovascular disease. Finally, we detail the importance of deep phenotyping and interactome networks and the use of this information for rational polypharmacy. These topics highlight the urgent need for precise phenotyping to advance precision medicine as a strategy to improve cardiovascular health and prevent disease.** (***Circ Res***. **2018;122:1302-1315. DOI: 10.1161/CIRCRESAHA.117.310782.)**

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It is because we are not exact that we fail

—Paul Ehrlich, 1896.[1]

Over the past 50 years, progress toward the eradication of cardiovascular disease has been achieved through the adoption of lifestyle modifications, including dietary, tobacco, and exercise interventions, as well as evidence-based therapies that aim to modify a recognizable and commonly shared cardiovascular or at-risk phenotype. Despite the success of this approach, the related issues of disease prevention and cure have been elusive, presumably because of imprecise deep phenotyping of individuals needed to characterize subgroups of disease. The magnitude of the problem remains considerable. At present, there are 92.1 million adults (>1 in 3) in the United States who have been diagnosed with cardiovascular disease, with a projection that by 2030, at least 44% of the adult population will have this diagnosis.[2] Although death rates attributable to cardiovascular disease have declined ≈25% from 2004 to 2014 in the United States, cardiovascular disease remains the leading cause of death worldwide accounting for ≈32% of all global deaths, with the expectation that this number will rise to >23.6 million deaths annually by 2030.[3,4] The contribution of attendant comorbidities and traditional risk factors (eg, hyperlipidemia, hypertension, diabetes mellitus, metabolic syndrome, and chronic kidney disease), health behaviors (smoking and tobacco use, physical inactivity, nutrition, overweight, and obesity), and other immutable factors (family history) to morbidity and mortality is understood and likely underlies the sex-, age-, race-, ethnic-, regional-, and economic-based differences in disease burden (reviewed in [4]). A recent meta-analysis stressed the importance of these comorbidities to disease risk. This study, which included data from 9 prospective cohort studies that followed 12 878 individuals, found that working toward optimal cardiovascular health metrics to achieve the greatest possible benefit was associated with a decrease in the risk for major adverse cardiac events, including cardiovascular mortality (relative risk [RR], 0.25; 95% confidence interval: 0.10–0.63).[5] Taken together, there is broad heterogeneity in the clinical profiles and outcomes of individuals with cardiovascular disease, thereby highlighting the urgent need for precision phenotyping.

The current approach to reducing cardiovascular morbidity and mortality in at-risk individuals or those with established disease is based on a traditional reductionist approach and uses a multitiered system with input from patients, the physician and the medical system, and evidence-based medicine at large. The first layer involves patient identification of symptoms that represent a deviation from normal or baseline.

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Nonstandard Abbreviations and Acronyms	
GWAS	genome wide association study
SNP	single nucleotide polymorphism

This report initiates entry into the medical system where contact with a physician results in a personalized assessment of the physical signs of disease and implementation of evidence-based therapies whose efficacy is supported by results from clinical trials. Although this paradigm of care can ameliorate symptoms and affect disease progression, this outcome is not always certain, especially when targeting a chronic complex illness like atherothrombotic cardiovascular disease that does not have a single root cause. To address this issue, it is necessary to understand the totality of cardiovascular disease at a granular and integrative molecular level.

Although all patients are fundamentally unique, reductionism in medicine presupposes that patients with common signs and symptoms share the same disease pathophenotype and, therefore, will respond similarly to medical, procedural, and behavioral interventions tested in aggregates of like individuals.[6–8] It also places the focus squarely on treatment of established cardiovascular disease without addressing health, prevention, timing of disease inception, or cure and eradication.[9] Owing to advances in panomics (genomics, transcriptomics, epigenomics metabolomics, proteomics, and microbiomics), that is, technologies and data analysis that provide in-depth clinical, biological, and molecular phenotyping, there is growing awareness that this conventional approach may be an overly simplistic view of the multiple contributors to and complexity of an individual's cardiovascular disease phenotype. Similarly, it is now understood that other factors, such as exposure to the natural, personal, and social environments, contribute to an individual's highly personalized disease phenotype (reviewed in [10]). Integration of this large body of data points lends itself toward a more exacting (patho)phenotype, one that is amenable to precision medicine.

Why precision medicine? Precision medicine represents a new strategy in the approach to care by targeting prevention and treatment while considering individual differences in genetics, exposures, and lifestyle and health factors that are determinants of a person's disease phenotype (Figure 1). The goal of precision medicine is to identify optimal care for an individual based on a unique personal profile rather than that of the average population. The power of precision medicine lies in the data and requires the synthesis of rapidly changing data sets, ranging from standard clinical, imaging, and laboratory testing to next-generating sequencing, metabolomics, and proteomic studies to historical health record data. Data derived from these sources may also be analyzed using advanced systems biology and network analytical methods to uncover new and unbiased relationships between health and disease factors. The optimal system will also evolve rapidly, learn, and be facile enough to be useful for prevention, diagnosis, and treatment across a broad range of cardiovascular health factors, risk factors, and diseases. The evolution of precision medicine and its application to cardiovascular disease hold the promise of improving health as well as revolutionizing prevention and treatment options similar to what has occurred in the field of oncology.

Population Averages and Probability Density Function

To move precision medicine into the cardiovascular arena, it is necessary to identify and adopt parameters that reflect what is a considered the normal or ideal range (Figure 2A). This is especially important given the diversity in population age and ethnicity where normal standards may change over time. Within the general population, there is variability with some individuals who have ideal health, others who have recognizable disease risk factors, and those who have established disease. Within groups, the transition between these health states tends to be less clear with there generally being a continuum with overlap between categories.[9] Examples of this point are blood pressure and blood cholesterol levels. In each case, there are individuals with normal levels who are considered healthy, those with increased levels in the absence of cardiovascular disease, those with high levels and disease, as well those who do not fit into any clear category, and are at an overlap of states.[9]

In clinical trials, this continuum of disease is often simplified with the assumption that all participants have the same phenotype, which can be represented using a typical bell-shaped curve with a discernable median measurement. Individuals entered in the clinical trial are considered based on the variable of interest, such as their cholesterol level, blood pressure, or history of myocardial infarction, and not their complex phenotype. This oversimplification allows results to be described in terms of an average finding on a per group basis. Although this paradigm has been the norm, the hazard of assuming similarity is that only relatively large differences may be detected as significantly different, and the actual range of responses may be undetected.[9] This concept was illustrated when patients with chronic heart failure were rephenotyped using cluster analysis. This analysis revealed significant heterogeneity between patients with individuals segregating into groups that would not have been predicted based on their initial clinical phenotype.[11] In precision medicine, similarity in phenotypes is not assumed for the purpose of studying a population behavior or response. Instead, the goal is to deviate from population averages as the metric and focus on the individual's unique phenotype with an eye toward identifying a response to treatment as one that moves the individual from disease to health and those at health to ideal health.[9]

Responses of the Tails of the Distribution and Implications

The importance of phenotyping and identifying an ideal level of health within community-based populations has implications for defining what constitutes a high-risk phenotype or those individuals who fall in the tail(s) of the distribution curve. For example, individuals with blood pressure or blood cholesterol levels at the population extreme are considered high risk. There have been 2 strategies considered when deciding how to reduce adverse events: a high-risk strategy and a population-based strategy. The high-risk strategy targets only those individuals who fall within

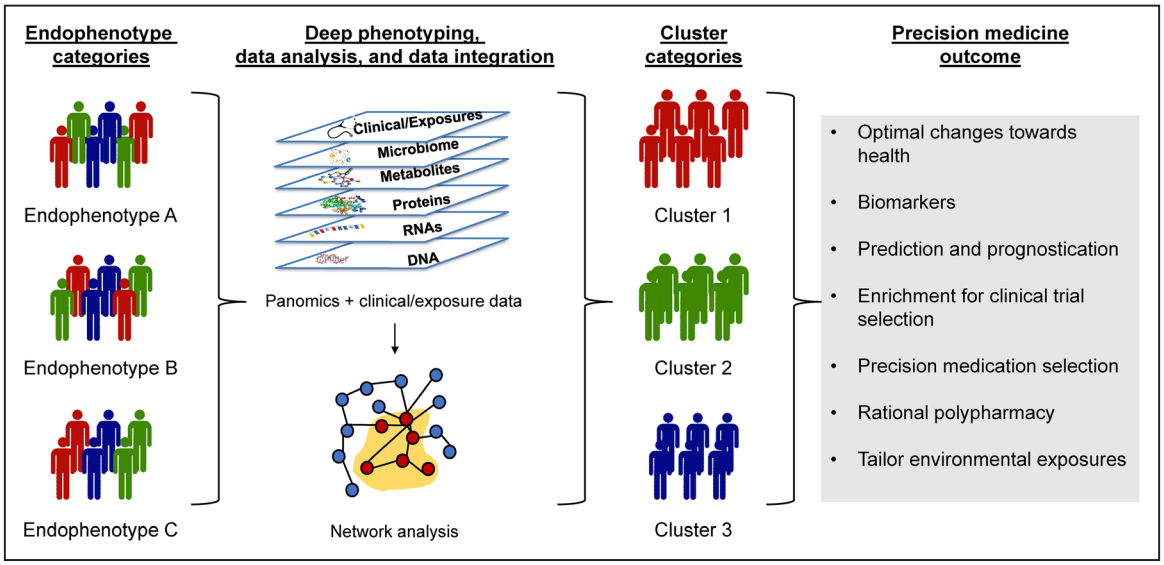

Figure 1. A precision medicine approach to phenotyping. Individuals may have a similar endophenotype but be biologically distinct and have different disease profiles. Using a precision medicine approach, individuals undergo deep phenotyping with data analysis performed using network analysis. This analytic strategy clusters individuals into groups that are different from those based on endophenotype alone. This methodology can be used to optimize medication and behavioral changes to improve health, predict and prognosticate disease, identify biomarkers for disease, enrich clinical trial enrollment, and optimally tailor exposures.

the tail of the distribution curve and have the greatest risk for disease in an attempt to lower levels to what is considered normal or ideal. However, the majority of cases of cardiovascular disease occur in individuals who fall in the average risk group. A population-based strategy targets this latter group, focuses on treating more individuals in the population, and aims for a smaller population-based risk factor reduction. This approach follows the argument put forth by Geoffrey Rose, viz, that shifting the risk distribution curve by only a small amount within a population will have greater societal benefit in reducing or preventing cardiovascular morbidity and mortality than treating only high-risk patients.[12] Others have also argued that significant reduction in the population burden of cardiovascular disease can only occur from a population approach shifting the entire population distribution to lower levels.[13] Despite the epidemiological cogency of this argument, adopting a population-based strategy that shifts the population mean also shifts the distribution of individuals who fall within the tails and, therefore, cross thresholds to initiate or stop treatment (Figure 2B). The net outcome can be either beneficial or harmful. Consider differences in the threshold for treatment of cholesterol using guidelines established by the American College of Cardiology/American Heart Association (ACC/AHA) as compared with the US Preventive Services Task Force. Differences in the guidelines suggest that shifting to the US Preventive Services Task Force recommendations from the ACC/AHA guidelines resulted in ≈9% of individuals who met ACC/AHA guideline criteria for statin use for primary prevention no longer being recommended for treatment; 55% of this group are younger adults with high mean long-term risk for cardiovascular disease.[14]

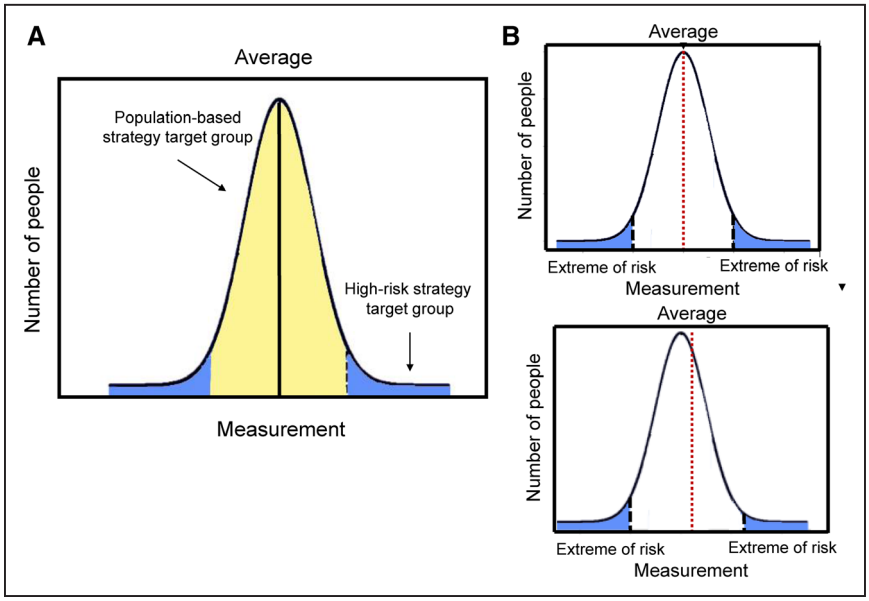

Figure 2. Population distribution and effect of changing the population mean. **A**, Within a population, the majority of people express a phenotype that centers around a mean with a minority of individuals who exhibit an extreme or high-risk phenotype. **B**, A change in the population average affects the number of individuals who are considered to be at the extremes. This may also influence the number of individuals who reach a predefined threshold for initiating treatment.

Using data from the National Health and Nutrition Examination Survey III study, investigators performed a head-to-head comparison of population-based and high risk-based treatment strategies using a low- or moderate-intensity intervention to determine which had the greatest benefit for reducing cardiovascular events and cardiovascular mortality. The study compared a population-based strategy that treated all, a high-risk strategy that selected individuals within the top 25% low-density lipoprotein cholesterol level, and a high-risk strategy based on individuals within the top 25% for cardiovascular risk as determined by a risk prediction tool. In this case, the investigators found that the high-risk strategy focused on individuals within the top 25% of cardiovascular risk was the most efficient method for preventing cardiovascular events over the long-term but was comparable to a population-based strategy with a more moderate interventional goal. This finding led to the conclusion that while the high-risk treatment strategy was the most efficacious, the population-based prevention strategy was a reasonable option if the intervention had no or minimal side effects.[13] In contrast, in developing low- and middle-income countries, the high-risk strategy should be used, especially when there are few resources available.[15]

Search for Single Pathogenic Genes/Gene Products and Its Flaws

The standard view that all or most cardiovascular diseases have a heritable component has fueled the search for single pathogenic genes for specific disorders. Although cardiovascular disease is significantly broad and encompasses diseases related to blood vessels, the myocardium, heart valves, the conduction system, and developmental abnormalities, there are only a few cardiovascular disorders that can be attributed to a single pathogenic gene. Nonetheless, there are notable examples of monogenic disorders that cause cardiovascular disease, such as a mutation in the low-density lipoprotein receptor (*LDLR*) gene that causes familial hypercholesterolemia,[16,17] in the β-myosin heavy chain and other sarcomeric proteins that are causal for hypertrophic cardiomyopathy,[18,19] and a mutation in the fibrillin (*FBN1*) gene that causes Marfan syndrome among others.[20] In contrast, atherosclerosis and myocardial infarction are multifaceted diseases with a complex inheritance, cannot be explained by a single pathogenic gene, and are more likely because of perturbations of large, and possibly phenotypically related, genes and other environmental factors.[21]

There are several inherent limitations associated with the search for a single pathogenic gene in complex cardiovascular diseases, and these are exemplified in known monogenic disorders. The first is that the genotype–phenotype relationship can be difficult to ascertain. For example, mutations in the α subunit of the type V voltage-gated sodium channel (*SCN5A*) was initially described as a single causal gene for inherited long-QT syndrome.[22] Since that time, other phenotypes have been associated with the mutation, including Brugada syndrome and dilated cardiomyopathy.[23,24] The second consideration involves penetrance and expressivity with examples of incomplete penetrance in a pedigree with familial hypercholesterolemia and an *LDLR* mutation, and differences in disease expression in families with Marfan syndrome and the same heritable mutation in *FBN1*.[25,26] Incomplete penetrance of these classic Mendelian disorders simply suggests other interacting genetic variants and environmental exposures on their pathogenesis.

The limitation of genome-wide association studies (GWAS) as a method designed to implicate a single pathogenic gene, or a limited number of pathogenic genes, is that performing genetic mapping by association only identifies genomic regions that may contribute to the disease process. Although coverage of the genome is improving, the singular information provided by these data are that a pathogenic gene resides nearby with distance determined by the sequencing platform. Results from GWAS support the concept that complex disorders possess genetic heterogeneity of variants (common, low-frequency, or rare), and this is likely the most frequent expression pattern in these types of diseases. This point was exemplified in a GWAS meta-analysis of individuals with myocardial infarction and control subjects. In this study of 60 801 individuals with a myocardial infarction and 123 504 controls, there were common and rare variants identified accounting for genetic heterogeneity.[27]

Another argument against a single pathogenic gene for atherothrombotic vascular disease and myocardial infarction is illustrated by the relationship between chromosome 9p21 and coronary artery disease or myocardial infarction. Single nucleotide polymorphisms (SNP) in 9p21 were identified by several independent GWAS, and each risk allele was associated with a 29% increased risk of cardiovascular disease.[28–30] The findings that the SNPs were in noncoding regions, the nearest genes were >100 Kb away, and causality between the nearest genes (*CDKN2B, CDKN2A*) and susceptibility to atherosclerosis have not yet been ascertained all argue against the single pathogenic gene explanation.[28–30] Considering the history of GWAS and the observation that these studies have not identified a single pathogenic gene or SNP as the mechanism underlying coronary artery disease or myocardial infarction indicates further that searching for a single element to explain a complex phenotype is not sufficient. Instead, it is more likely that results from GWAS and next-generation sequencing will contribute to a mechanistic exploration of molecular networks (see below) and to the need for concomitant deep phenotyping multifaceted cardiovascular diseases, such as coronary artery disease and myocardial infarction.

Resilience and Mendelian Disease Genes

Advances in next-generation sequencing have expanded our understanding of the genetic basis of cardiovascular diseases in particular and of all human disease in general. There are >150 000 disease-related genetic variants mapped to >6000 Mendelian disorders (Online Mendelian Inheritance in Man) that have been catalogued in the Human Gene Mutation Database.[31,32] Although this information is readily available, there are relatively few therapies developed that effectively treat or cure these Mendelian diseases.[33] For common complex diseases, such as atherothrombotic cardiovascular disease, few gene variants have translated directly into predictors of disease risk or severity, thereby limiting their potential to be developed into a diagnostic or therapeutic.

More recently, attention has turned to examining the genetic and environmental factors that predispose to resilience, the ability to adapt successfully to stress. In the context of

Mendelian disease, resilience implies the ability to withstand changes to fitness in the presence of disease-associated mutations.[34] The role of second site mutations or environmental modifications that promote resilience to disease has also been established in preclinical models.[35,36] In addition, clinical studies that have found highly penetrant disease-causing mutations in individuals who do not manifest the disease phenotype, suggesting that there are either genetic or environmental resilience factors that protect individuals from manifesting disease.[37,38] A healthy lifestyle, defined as the absence of obesity, no current tobacco use, a healthy diet, and regular physical activity, has been shown to serve as an environmental resilience factor and modify genetic risk of cardiovascular disease. In a study of 55 685 individuals who were stratified according to a polygenic risk score comprised 50 SNPs associated with coronary artery disease, individuals with a high genetic risk with a healthy lifestyle had a 46% reduction in the relative risk of coronary events.[39]

Although many genetic studies have attempted to identify mutations linked to disease, an alternative is to search for genetic factors that prevent disease, or wellness factors, in the presence of Mendelian disease-causing mutations. Although attempts to find resilience factors have been limited, some secondary cardiovascular disease modulators have been identified, including a loss-of-function mutation in proprotein convertase subtilisin/kexin type 9 and mutations in zinc transporter 8 that protect obese individuals from diabetes mellitus.[35,40–42]

A more recent study used a different tactic to find resilience factors and studied the genomes of 589 306 individuals who were apparently healthy. Using this approach, they identified 13 adults with what had been viewed as completely penetrant Mendelian disease mutations for 8 different severe childhood diseases, including cystic fibrosis, atelosteogenesis, and Smith–Lemli–Opitz syndrome, but who were without any clinical manifestations of disease. This finding suggested that these individuals have some form of genetic protection or resilience against even these classical Mendelian disorders; however, it was not possible to isolate the resilience factor(s) because of the data available and study design.[43]

Search for the Ehrlichian Magic Bullet and Its Flaws

The complexities of the cardiovascular disease phenotype also highlight the fact that there is no single therapy, or Ehrlichian magic bullet, that will cure a disease. In 1900, the German Nobel laureate Paul Erlich, a pioneer of chemical biology and chemotherapy, put forth the concept of the magic bullet. He hypothesized that there would be a way to target specifically disease-causing microbes in the same way a bullet fired from a gun hits its target. He referred to this hypothetical agent as Zauberkugel or magic bullet. His continued work to cure syphilis using a magic bullet led to the discovery of Salvarsan (an arsenical compound) on August 31, 1909, the 606th compound he tested that was efficacious and free of important side effects.[44]

The magic bullet concept was soon popularized, and its meaning expanded to include a perfect drug to cure a specific disease that acted without side effects. The goal would be achieved by identifying a compound that targets a specific disease-related molecule and does so in a highly specific manner with no off-target effects. This idea has become an enduring part of cardiovascular (and all of) medicine even though there are numerous examples of therapies or interventions for cardiovascular disease that have been hailed as a magic bullet yet have failed to provide a cure, including stem cells and statins. In fact, this is not surprising because cardiovascular diseases are complex pathophenotypes with significant biological diversity owing to numerous genetic, metabolic, and environmental mediators.

Thus, the idea of a single target in the original, strictest definition of a magic bullet is unlikely to have broad applicability in cardiovascular diseases. In other words, the use of a mono-specific drug(s) to target a multifactorial disease will not be successful. This has led to the idea of targeting multiple targets at once (eg, the polypill). Although this strategy may improve the pharmacological profile, there is also the increased risk of adverse effects. Biologicals such as monoclonal antibodies are less likely to have off-target effects but may show variations in efficacy and unknown off-target effects or on-target toxicity (eg, abciximab and severe bleeding or immune checkpoint inhibitors and autoimmune diseases). This approach has evolved further to fall within the rubric of precision medicine via network-targeted therapy that uses a combination therapy strategy targeting multiple steps in a signaling pathway or network identified by deep phenotyping. This more complex approach could be considered a modern interpretation of Ehrlich's magic bullet theory in the contemporary era.[44,45]

Importance of Molecular Interaction (Interactome) Networks

Using data from genomic and other panomic profiling, data can be analyzed using molecular interaction or interactome networks to discover disease associations and possible therapeutic targets (Figure 3). Interactome networks play an increasingly important role in the discovery of novel relationships between genes or proteins that may have broad applicability across a spectrum of human diseases. The interactome defines a comprehensive, unbiased set of biologically relevant molecular (ie, gene, protein, metabolite) interactions in a cell, organ, or person. The advantage of examining the interactome to understand disease pathobiology is that the interactome allows for the simultaneous consideration of (ideally) all or a large number of relevant genes, metabolites, and proteins, as well as their interactions as depicted through network representation. These networks and subnetworks allow for discovery of new interactions, ascertainment of pathways governing phenotype, identification of critical regulatory checkpoints in a biological system, and prediction of the consequences of disease in network associations or pathway functions on phenotype. The interactome eliminates the bias introduced by analyzing a data set using a reductionist approach, which examines a limited number of interactions in the data set to find a differentially expressed gene or protein associated with a phenotype without consideration of the network context within which it operates.[46,47] The current human protein–protein interactome contains 13 460 proteins that have 141 296 physical interactions (protein–protein, metabolic pathways, and kinase

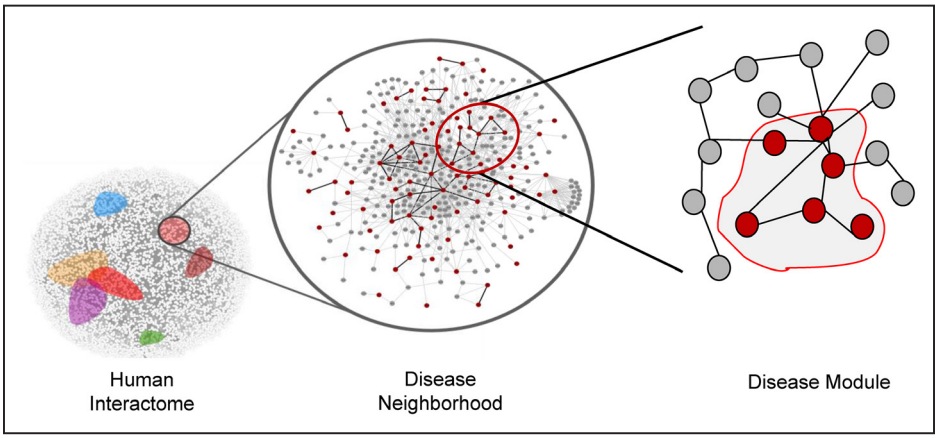

Figure 3. Molecular interaction networks (interactome). The protein–protein interactome describes interactions between proteins in a scale-free (ie, interactions are not random but clustered) manner. Within the interactome, groups of proteins reside in disease neighborhoods (colored areas) that may overlap indicating common mediators (**left**, center). Within the neighborhood, there are several disease modules or groups of protein interactions that are related. Analysis of the interactome may uncover new or previously unrecognized relationships. Gray circles, nodes (ie, proteins in a protein–protein interaction network); black lines, edges (ie, interactions).

substrate).[48] The interactome network is scale free, indicating that interactions are not random, and the proteins within it exhibit emergent behavior such that detailed information about 1 protein does not predict its functional response within the context of the interactome or of the interactome itself.[49] Although the human interactome is incomplete owing to the fact that the majority (80%) of pairwise protein interactions have not been analyzed using currently available high-throughput methodology, it remains a valuable tool for discovery of disease-related phenomena.[48]

The human interactome has been shown to contain subnetworks for specific diseases, so-called disease modules. Certain disease modules overlap with one another, and these diseases typically have similar symptoms, patterns of coexpression, and comorbidities while diseases that reside in separate neighborhoods in the network do not share these characteristics and are clinically distinct. Analysis of disease relationships has shown that 7% of disease pairs have overlapping disease neighborhoods in the interactome with unexpected disease relationships, such as that between asthma and celiac disease, which may share a molecular phenotype despite differences in their pathobiology. Interrogation of the shared factors between asthma and celiac disease revealed pathways for immunoglobulin A production as a common intermediary.[33] Interactome-based network analysis has been used to inform GWAS data. For example, the great majority of genes associated with type 2 diabetes mellitus have small effect size and limited statistical significance when analyzed in isolation; however, mapping these alleles to the interactome leads to the identification of novel interactions in pathway clusters that provide unique, highly statistically significant information on mechanism not appreciated by conventional GWAS (Figure 4). Another capability of the interactome is to improve comprehension of the molecular actions of drugs with a goal of identifying drug targets, the potential for adverse reactions, and the possibility of repurposing drugs based on newly identified relevant molecular targets. This concept was investigated for myocardial infarction using a network that incorporated myocardial infarction disease genes, drugs, drug targets, and drug target interactors or binding partners in the interactome to reveal that many myocardial infarction–related drug targets and disease proteins have close relationships within the disease module in the interactome, and some of the drug target intermediaries are themselves targets for other drugs suggesting potential drug repurposing strategies.[50] Studies of the interactome have also been used to identify tissue specificity of modules associated with human disease. This has shown that an entire functional subnetwork or pathway incorporating disease gene products, or a disease module, must be expressed within a particular tissue for a disease to be manifest in that tissue, not simply expression of the disease gene product itself. This type of analysis also leads to the creation of a disease–tissue network and allows for the discovery of unexpected disease–tissue associations.[51]

Importance of Phenotype

A core principle of precision medicine is establishing the precise phenotype for any given disorder (Figure 5). The ability to understand and recognize the relationship between the elements that comprise health phenotypes and disease (patho) phenotypes is required for precision medicine to improve individual and population outcomes.[52,53] The foray into precision phenotyping has faced some obstacles, including the unknown function of many genes or metabolites, the incomplete descriptors used to categorize diversity within disease phenotypes, and inadequate data collection or extraction from medical records.[52,54] These shortcomings have led to the characterization of most phenotype descriptions as imprecise and highlight the necessity of a unified descriptive ontology that is widely adopted. This widely recognized need has led to the proposal that the Human Phenotype Ontology be used as a standard to characterize disease phenotypes using a specific vocabulary; however, it remains to be seen if this system will achieve widespread use.[55]

The importance of obtaining a more detailed, granular phenotype for cardiovascular diseases is underscored by the fact that phenotypic profiling is lagging with respect to panomics technologies, and, that phenotypic information is necessary

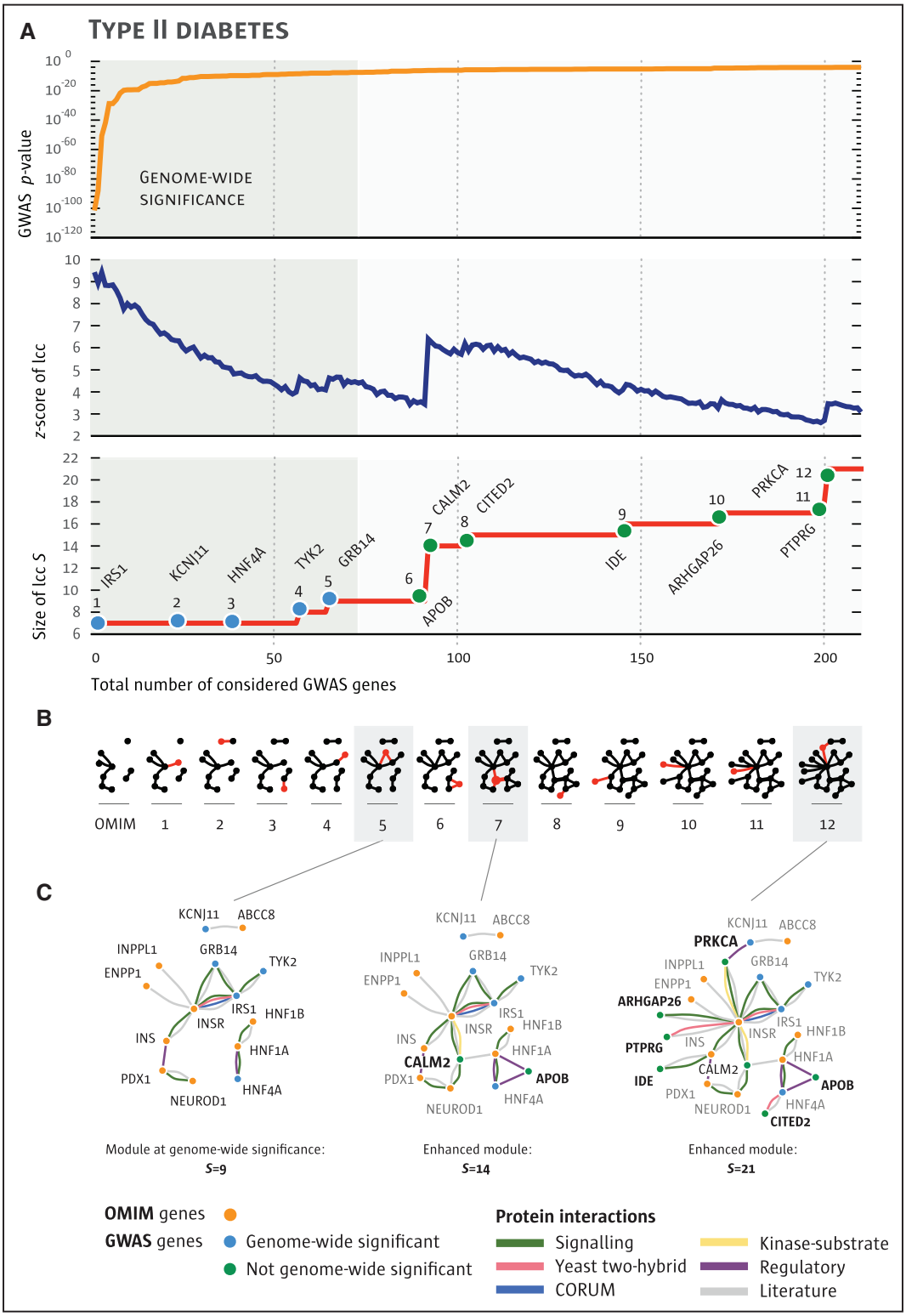

Figure 4. Identifying genome-wide association studies (*GWAS*) genes that have biological relevance. Analysis of GWAS data reveals that there are a large number of genes that, while having genome-wide significance, have modest effect sizes. **A**, Using data from patients with type 2 diabetes mellitus as an example and starting with a module that includes 6 genes of greatest statistical significance, *GWAS* genes are added to the module in decreasing order of their *P* value (**top**). The statistical significance of the growing network as compared with a random network is shown (**middle**) as well as the size of the resulting module (**bottom**). **B** and **C**, Of 77 significant GWAS genes, only 5 connect to the interactome cluster initially; however, the addition of the interactor gene (product), *CALM2*, joins disconnected parts of the network and increases both its size and significance. Another disconnected cluster is then joined to the module through consideration of 200 GWAS genes, including the *KCNJ11* (GWAS significant gene) and *ABCC8*. Reproduced from Menche et al[48] with permission. Copyright ©2015, American Association for the Advancement of Science. OMIM indicates Online Mendelian Inheritance in Man.

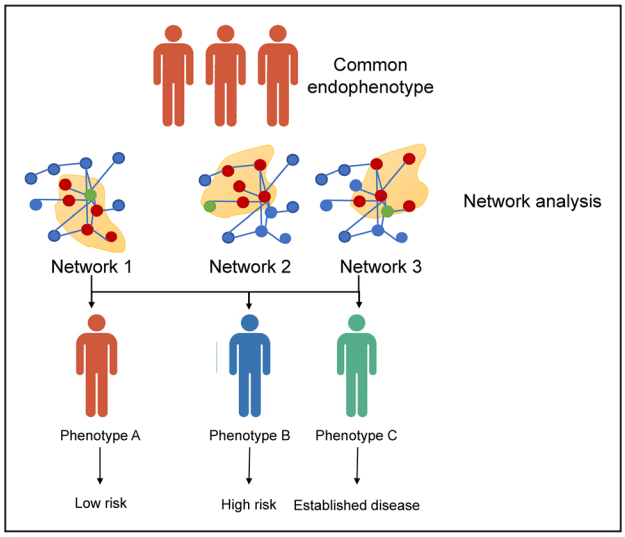

Figure 5. The importance of phenotype and its molecular network underpinning. Individuals who share a common endophenotype, such as hypertension or hypercholesterolemia, may have a different phenotype when examined at a molecular level. Using molecular phenotyping, such as genome sequencing, and network analysis, individuals may cluster into distinct phenotypes. These phenotypes have important implications for disease risk, prognosis, or response to medication. These important differences are not discoverable when relying on endophenotype alone (blue nodes, normal or major alleles; red nodes, variant or minor alleles in protein–protein interaction network).

to deconvolute the results of genomic, transcriptomic, metabolic, and proteomic studies. Only recently has the approach to clinical phenotyping moved beyond historical metrics, such as blood pressure, to improve stratification of cardiovascular diseases. Current phenotypic assessments are beginning to incorporate standard clinical traits, such as blood pressure, as well as other complex characteristics, like social, environmental, and personal exposures.[10,56] Phenotypes are also being assessed continually using personal sensors and wearable devices, illustrating the importance of time trajectories in monitoring early identifiers of disease progression.[57,58]

There are several recent examples of the use of advanced phenotyping methodologies to discover differences within individuals with a clinical syndrome that has underlying heterogeneity. Clinical phenomapping of patients with heart failure and preserved ejection fraction using unbiased hierarchical clustering analysis revealed 3 distinct groups of patients, with 1 phenogroup having an increased risk of heart failure hospitalization (hazard ratio: 4.2; 95% confidence interval: 2.0–9.1; $P<0.001$).[58] Similarly, cluster analysis of 1619 patients with chronic heart failure identified heterogeneity within the group as a whole and 4 phenotypic clusters of patients with differences in their risk of all-cause mortality or all-cause hospitalization.[11]

The concept of an unbiased or undirected phenome-wide assessment of an individual is also entering the realm of possibility and has been conducted in a single person who was extensively phenotyped during the course of 18 months. In the MyConnectome project, brain function over time was assessed with imaging, functional studies, health surveys, and genomic and metabolomic profiling with data from the latter examined using network analysis. Using this platform, gene and metabolite expressions were related to dynamic changes in brain connectivity over a timescale of days to months. This pioneering study illustrates the feasibility of this deep temporal phenotyping approach and provides a strategy for translating these types of studies into the cardiovascular space.[59]

Endophenotype Diversity and Pre-Emptive/Preventive Strategies

The endophenotype, or intermediate phenotype, is a biological trait that is quantitative and reflects the function of a biological system. It is heritable and is more closely related to the root cause of a disease than the broad clinical phenotype.[60,61] GWAS that examine conventional phenotypes can be improved upon by focusing on individual endophenotypes.[62] Endophenotypes are themselves thought to be subject to natural selection leading to the concept that there are evolutionarily established molecular mechanisms, which regulate endophenotypes, and that these factors translate into genetic predisposition for the correlate downstream clinical phenotypes.[63–65] This view leads to the expectation that complex molecular mechanisms link genes responsible for both endophenotypes and phenotypes.[66] Thus, genetic effects on endophenotype and phenotype do not necessarily have to be the same in different populations, and genetic predisposition to an endophenotype does not necessarily translate into predisposition for a downstream phenotype.

Several GWAS studies have illustrated the diverse relationships between endophenotypes and phenotypes. For example, 1 study examined the association of the rs693 and rs562338 polymorphisms in the apolipoprotein B locus with total cholesterol and high-density lipoprotein cholesterol (endophenotype) with myocardial infarction and survival (phenotypes) across 4 population-based studies (MESA [Multi-Ethnic Study of Atherosclerosis], ARIC [Atherosclerosis Risk in Communities], FHS [Framingham Heart Study], CHS [Cardiovascular Health Study]). The endophenotypes were investigated to determine whether they could mediate the associations of the polymorphisms with myocardial infarction or mortality. In this analysis, the SNPs rs693 and rs562338 were robustly associated with the endophenotype (total cholesterol) but had a trivial association with the phenotype (myocardial infarction and survival) despite the well-known relationship between lipids and myocardial infarction.[67]

Network analysis has been used to examine endophenotypes and their overlapping relationships to different diseases. Inflammation, thrombosis, and fibrosis are endophenotypes that are linked pathologically and common to virtually all disease states, both in terms of response to injury and to repair.[68–71] To explore biological and topological crosstalk between these endophenotypes, network analysis of the inflammasome, thrombosome, and fibrosome was undertaken. Mapping these networks to the human interactome identified inflammation, thrombosis, and fibrosis subregions that were highly overlapping and contained disease genes associated with complex diseases and cardiovascular risk factors. These subregions were found to be integral to the structure of the basic interactome network, thereby highlighting the key role of these processes in (health and) disease.[72]

With the advent of panomics profiling, endophenotypes and their association with complex disease phenotypes will be refined further. To ensure the integrity of these relationships, however, there is an implicit need for standardization of methodology and platforms, as well as adoption of CLIA (Clinical Laboratory Improvement Amendments)–grade laboratory testing with strict adherence to quality control. Analytical methods to integrate endophenotypic data should favor unbiased approaches, such as network analysis, and account for issues related to multiple testing, which is an inherent limitation of large data set analysis.

Genetic Diversity and Rational Polypharmacy

Although randomized clinical trials have determined the efficacy of many new therapeutics across large populations of individuals with similar clinical phenotypes, heterogeneity in the response to drugs remains a relevant and challenging issue. Aggregating patients with similar disease characteristics into a cohort deemed to be putative therapeutic responders with equal effect obviously ignores this heterogeneity for clinical trial design and therapeutic simplicity even though there is no phenotypic basis to support such an oversimplified categorization (Figure 6A).[56] Pharmacogenetic variation because of single and cumulative drug–gene interactions can lead to adverse drug interactions[73,74]; these types of reactions increase with polypharmacy. Approximately 66% of adults age ≥65 years have at least ≥1 prescription medications that require daily use.[75–77] It is estimated that ≈35% of geriatric patients have adverse drug events, at least half of which are deemed preventable; and 10% to 17% of hospitalizations in this population are related to drug reactions leading to 51% of adverse drug–related deaths.[77–79] The application of precision medicine to this problem has revealed that cardiovascular pharmacogenetics can be used to identify genetic diversity markers associated with poor response or adverse reactions to drugs. In fact, drug interactions related to predisposing genetic factors lead to ≈47% of warnings of potential interactions associated with side effects.[79]

There are numerous examples of genetic diversity and DNA variants as determinants of response to a drug. In cardiovascular disease, platelet aggregation promotes atherothrombotic vascular disease and stent thrombosis after percutaneous coronary intervention. The P2Y12 inhibitor clopidogrel, which is part of a typical dual antiplatelet regimen, has a range of interindividual variability. Some individuals are known to be clopidogrel nonresponders, a phenotype that has been associated with genetic determinants and an increase in ischemic events.[80–83] Loss-of-function alleles in CYP2C19 (CYP2C19*2 and CYP2C19*3) have been associated with poor drug responsiveness while the gain-of-function allele CYP2C19*17 is associated with increased bleeding risk.[84–86] Attempts to use this information for tailored therapy in patients with drug-eluting stents and high on-treatment platelet reactivity, however, did not affect cardiovascular death, myocardial infarction, or stent thrombosis.[87]

It has been suggested that ≈50% of patients taking statins stop taking their medications owing to side effects or adverse events.[88] Of the related genes, only the gene for the soluble

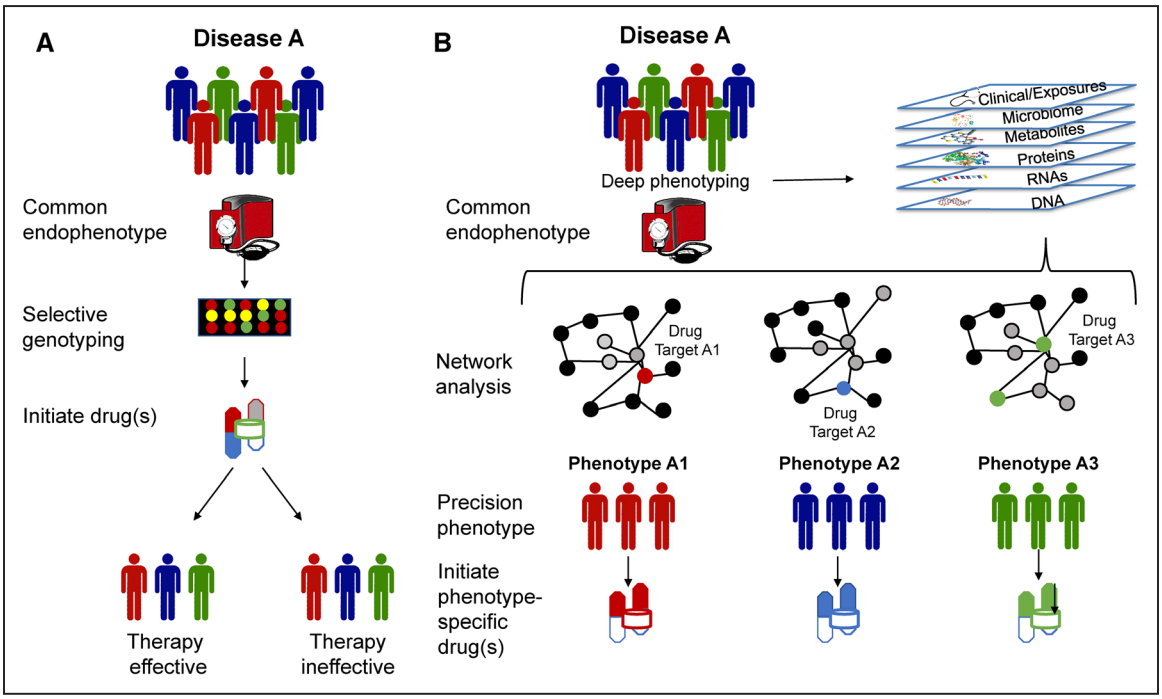

Figure 6. Precision medicine approach to rational polypharmacy. A, The current approach to selecting pharmacological therapy involves identifying a group with a common endophenotype, using genomic profiling in select cases to identify potential drug (non) responders, and then testing a medication based on results from clinical trials. **B**, Using a precision medicine approach, individuals with a common endophenotype undergo deep phenotyping, including panomics, exposures, and clinical assessments, and the data are analyzed using network analysis to identify more precise phenotypes and their molecular determinants in the interactome (gray nodes, disease-determining module on network; red, blue, and green nodes, drug targets by phenotype). This information is then used to select agents that target key pathways or proteins.

carrier organic anion transporter 1B1 (*SLCO1B1*), which regulates statin influx and metabolism in the liver, has been associated consistently with myopathy.[88] Patients who are either homozygous or heterozygous for the rs4263657 polymorphism have an increased risk for rhabdomyolysis with statin use, and it has been suggested that individuals with this SNP avoid statin drugs.[89]

Warfarin, one of the most commonly prescribed anticoagulants, has a narrow therapeutic window but wide interindividual variation.[90] Warfarin is metabolized primarily in the liver by oxidation by cytochrome P450 2C9 (*CYP2C9*) and inhibits the protein vitamin K epoxide reductase complex subunit 1 (*VKORC1*).[91,92] Studies have attributed the ≈10% to 50% variability in dose requirements to genotypes, notably SNPs in *CYP2C9* (*CYP2C9*2, CYP2C9*3*) and *VKORC1* (rs9923231).[93–95] The Food and Drug Administration has recognized the importance of these genetic variants and updated the drug packaging to include information on dosing based on *CYP2C9* and *VKORC1* genotypes.[96,97] Two randomized clinical trials, the COAG (Clarification of Optimal Anticoagulation through Genetics) trial and the EU-PACT (European Pharmacogenetics and Anticoagulant Therapy-Warfarin) study, evaluated genotype-guided warfarin dosing.[98,99] These studies incorporated *CYP2C9* and *VKORC1* genotyping into the clinical algorithm for selecting the warfarin dose. The 1015 patient COAG trial reported that genotyping had no effect on the percent of time in the therapeutic international normalized ratio range while the 455 patient EU-PACT study found that genotyping was useful, resulted in fewer episodes of excess anticoagulation (international normalized ratio levels ≥4.0), and led to more rapid achievement of the therapeutic range (21 versus 29 days) than those who were not guided by genotype.[98,99] The differences observed between these trials has been attributed to trial design, prevalence of the SNPs in the study population, and the demographics of the study populations.[100]

Genetic variants have also been identified that modify the response to other relevant cardiovascular drugs, including β-blockers (*ADRB1, ADRB2, GRK5, GRK4*); angiotensin-converting enzyme inhibitors (*ACE, AGTR1*); diuretics (*ADD1, NPPA, NEDD4L*); and calcium channel blockers (*CACNB2, CACNA1C*; reviewed in [101]). To date, however, genetic testing has not been used routinely to guide selection of these drugs, and many genetic variants require confirmation in larger studies.

Other pilot studies have examined the efficacy of implementing pharmacogenetic profiling coupled with a clinical decision support tool in polypharmacy patients to reduce adverse drug reactions and emergency department visits. In a small study of 110 patients randomized to genetic profiling of CYP 450 genes and prescribed relevant medications, the use of pharmacogenetic profiling was associated with a reduction in the number of emergency department visits (RR, 0.58; 95% confidence interval: 0.34–0.99; P=0.045) and hospitalizations at 60 days (RR, 0.48; 95% confidence interval: 0.27–0.82; P=0.0007). Interestingly, of 124 recommendations on drug therapy based on pharmacogenetic profiling that were passed on to the patient's clinician, only 96 (77%) were followed. Although exploratory, this study highlights the benefits of identifying genetic diversity to achieve rational polypharmacy and clinician attitudes toward this approach.[102]

Pharmacogenetic profiling has also been used to determine whether individuals treated with polypharmacy tend to express more rare variants than the general population and, therefore, are less likely to respond to individual medications. Using a deidentified electronic medical record and corresponding samples from a biorespository, investigators identified 326 frequently medicated individuals (defined as prescribed clopidogrel or warfarin in addition to >5 medications from select classes with at least 1 drug known to have a pharmacogenetic interaction). Analysis found that most of the marker allele frequencies in polypharmacy patients did not differ from what was reported for individuals of European descent in the 1000 Genomes Pilot with a single exception in *CYP2D6* (rs1080985).[103] The relevance of this finding was deemed unclear because it was not certain whether it was the result of sequencing errors in the 1000 Genomes Pilot or a true difference.[104]

Precision medicine will advance this field by using enhanced phenotyping for disease stratification to identify groups of patients that differ in drug responsiveness, will benefit from existing pharmacotherapies, or will benefit from rational polypharmacy (ie, the use of multiple drugs chosen based on knowledge of their interactome-based network location and effects on key pathways in the interactome that govern pathophenotype [Figure 6B]).[105] This strategy can also be used to identify biomarkers to guide drug dosing, continue therapy, or limit side effects and adverse drug reactions.[101] When and how pharmacogenetic profiling will become a mainstay of clinical practice to guide polypharmacy and limit adverse drug reactions remains to be determined.[106] In part, the slow uptake of clinically applied pharmacogenetics is a reflection of statistical uncertainty, the abundance of genomic variants (even those previously thought to be causative), and the typical association analysis rather than network analysis of the functional consequences of the variants.[107]

Precision Versus Personalized Medicine

Although the terms precision medicine and personalized medicine have been used interchangeably, they are not identical but, rather, related and overlapping disciplines. Precision medicine identifies the unique aspects of an individual related to health and disease to select appropriate and effective therapy. Personalized medicine may refer to implementation of these data into a person-specific treatment plan or, simply, the creation of a treatment plan for an individual based on a known biomarker(s). Personalized medicine is not, however, meant to suggest that results from detailed phenotyping will be used to create new drug or other therapies.

Precision medicine is increasingly considered as the art and science of creating individualized assessments of health and disease that are derived from established clinical and pathological indices integrated with state-of-the-art panomic (ie, genomic, transcriptomic, metabolomic, and proteomic) profiling.[108,109] Thus, precision medicine aims to drive the field away from the implementation of the same pharmacotherapy, lifestyle intervention, or behavioral modification to a group of individuals presumed to share the same phenotype and toward

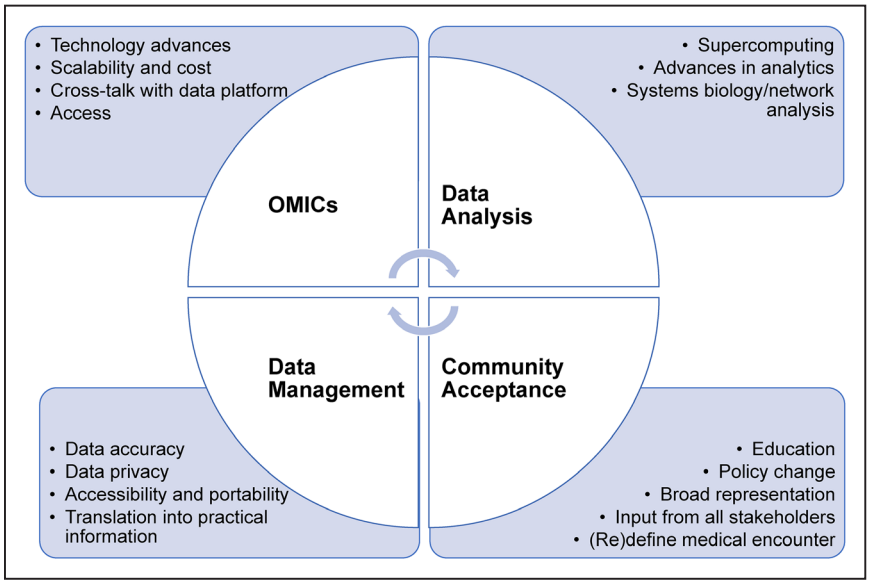

Figure 7. Challenges in precision medicine. Precision medicine relies on integration and dynamic adaptability of panomic analysis, overall data analysis, and data management; and acceptance by the public, medical, research, big pharma, and policy-maker stakeholders.

personalizing treatments that are aimed at prevention, promotion of health, and amelioration of disease. Although this concept has been embraced with success in the field of oncology, the issue of patient adherence with a personalized therapy identified using precision medicine remains a concern.[109] Estimates indicate that approximately half of all medications are not taken as prescribed and that patients with chronic conditions, such as cardiovascular disease, only take 50% to 60% of the medications prescribed.[110] Although this is a valid point and developments in precision and personalized medicine must be matched by patient education and acceptance of these strategies, it is also plausible that poor adherence rates are the result of imprecise medication use leading to limited efficacy and increased side effect risk in a given individual. This issue will clearly require further study.

Future Considerations

Precision medicine is poised to become the next great revolution in the practice of medicine, as well as in the maintenance of cardiovascular health and the prevention and cure of cardiovascular disease. Precision medicine disrupts standard practice and draws from clinical testing, electronic health records, panomics profiling, big data sets, and novel analytical methods, such as systems biology and network science, to create a person-specific phenotype that can then be used to identify an optimal intervention with minimal risk. The obvious benefits of this approach to patients, clinicians, and researchers are numerous and include individual phenotype specificity, identification of individuals with a similar molecular phenotype, selection of best drugs or therapies with maximal efficacy and no or limited adverse reactions, efficient selection and enrichment of clinical trial participants, potential to improve adherence and reduce costs, and creating a paradigm shift in how cardiovascular care is delivered. To accomplish this laudable goal, the medical community at large and other stakeholders will need to overcome barriers to implementation that range from technical to sociopolitical (Figure 7).[111] At the least, precision medicine will need to demonstrate that phenotype-based person-specific interventions are superior to the current standard of care and, ultimately, have a population effect by moving the mean on the disease spectrum toward health.[111] Other barriers are related to large data set collection and focuses on methods to ensure data accuracy, computational power, security and privacy of data sets, renewal of accruing data, and continuous development and refinement of analytical methods. Finally, education, affordability, and public acceptance of the strategy all play key roles in its ultimate implementation.[111]

Despite a clear path forward toward mainstream application of precision medicine, there continues to be debate about whether a precision medicine approach will have a global impact on cardiovascular disease prevention and treatment or will only serve a small group of patients and be relegated to a highly selected niche role. This skepticism has arisen, in part, based on progress in the field to date and perceived challenges in maintaining the physician–patient relationship.[112,113] Although these concerns are valid points, they are not insurmountable and are currently being addressed conceptually as how best to implement precision medicine in the practice of cardiovascular medicine. The nascent field of precision medicine fully embraces Paul Ehrlich's concept that imprecision leads to failure and harnesses our most precise technologies and methodologies to improve cardiovascular health and treat disease.

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