Circulation: Genomic and Precision Medicine

AHA SCIENTIFIC STATEMENT

# Interdisciplinary Models for Research and Clinical Endeavors in Genomic Medicine

## A Scientific Statement From the American Heart Association

**ABSTRACT:** The completion of the Human Genome Project has unleashed a wealth of human genomics information, but it remains unclear how best to implement this information for the benefit of patients. The standard approach of biomedical research, with researchers pursuing advances in knowledge in the laboratory and, separately, clinicians translating research findings into the clinic as much as decades later, will need to give way to new interdisciplinary models for research in genomic medicine. These models should include scientists and clinicians actively working as teams to study patients and populations recruited in clinical settings and communities to make genomics discoveries—through the combined efforts of data scientists, clinical researchers, epidemiologists, and basic scientists—and to rapidly apply these discoveries in the clinic for the prediction, prevention, diagnosis, prognosis, and treatment of cardiovascular diseases and stroke. The highly publicized US Precision Medicine Initiative, also known as All of Us, is a large-scale program funded by the US National Institutes of Health that will energize these efforts, but several ongoing studies such as the UK Biobank Initiative; the Million Veteran Program; the Electronic Medical Records and Genomics Network; the Kaiser Permanente Research Program on Genes, Environment and Health; and the DiscovEHR collaboration are already providing exemplary models of this kind of interdisciplinary work. In this statement, we outline the opportunities and challenges in broadly implementing new interdisciplinary models in academic medical centers and community settings and bringing the promise of genomics to fruition.

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We begin by distinguishing genomic medicine from clinical genetics: Whereas the former is an area of active research investigation and, with a few exceptions, has yet to be translated to the clinic, the latter is a well-established discipline in cardiovascular medicine. Clinical genetics has focused on highly penetrant variants in single genes resulting in diseases that are inherited within families in a mendelian fashion, for example, autosomal dominant or autosomal recessive. For the most part, clinical genetics has been used in the care of patients who have already been diagnosed with or are suspected to have classic mendelian diseases such as cardiomyopathies, channelopathies, familial dyslipidemias, and aortic disorders. Genomic medicine seeks to use larger-scale data obtained on sets of DNA sequences or other types of molecules, typically with the goal of improving the prediction, prevention, diagnosis, prognosis, and treatment of more common forms of cardiovascular diseases and stroke. In this statement, we focus on genomic medicine.

We also distinguish between genomic medicine and precision medicine. Although the two are clearly intertwined, it is perhaps best to view genomic medicine as the subset of precision medicine that focuses on molecular variation. Precision medicine has been described in a recent commentary as an integration of 6 "dimensions" that describe individuals: "omic" data, the microbiome, health system data, study participant–generated data, motivations and behavior, and the exposome/social determinants.[1] For the purpose of this statement, genomic medicine studies will be regarded as those that interrogate associations between the first 2 dimensions, omic data and the microbiome, and clinical phenotypes as captured by the third and fourth dimensions, health system data, most readily (but not exclusively) obtained via electronic health records (EHRs), and study participant–generated data.

Although definitions vary widely among different observers, for the purpose of this statement, we regard genomic data as including both the omic and microbiome data because both reflect molecular variation. Omic data include the information within the genome—the DNA sequence content within the 46 chromosomes in the nucleus of a human cell and extranuclear chromosomes within mitochondria—and the information within the expressed genome, which encompasses epigenomics (DNA and chromatin modifications), transcriptomics (RNA), proteomics (proteins, including those with posttranslational modifications), metabolomics (metabolites), and potentially other types of omic data that reflect molecular variation at the human cellular level.[2–4] The microbiome encompasses genomic profiling of nonhuman cells within the human body (metagenomics), most notably the bacteria within the gastrointestinal tract but also bacteria in other anatomic locations, fungi, archaea, and viruses.[5]

Although a person's germline genome, being encoded in DNA, is largely stable throughout the body for the person's lifetime (with a few exceptions such as cancer) and can be assessed with any tissue, the expressed genome can vary substantially across tissues and even within a single tissue over time. Therefore, it should be recognized that cardiovascular genomic research that involves the measurement of the expressed genome is best served by the use of tissues directly involved in cardiovascular diseases (eg, cardiomyocytes, hepatocytes, and vascular endothelial and smooth muscle cells), which are difficult to procure and have not been studied extensively to date, rather than tissues that are more commonly studied because of ease of access but are of less relevance to cardiovascular diseases (eg, peripheral blood mononuclear cells). This remains an important limitation at the present time.

## GENOME-WIDE ASSOCIATION STUDIES

The completion of the Human Genome Project in 2003, in tandem with the cataloging of common DNA variants (ie, DNA variants with minor allele frequencies higher than a few percent in a given population) throughout the human genome,[6,7] empowered the genome-wide association study (GWAS) design, which was first successfully performed and reported in 2005.[8] Knowledge of these variants enabled the production of genome-wide genotyping arrays, or chips, that interrogate variants at hundreds of thousands of locations in the genome in a sample of human DNA in a single experiment at a relatively inexpensive cost (compared with DNA sequencing). The goal of GWASs is to identify, in an unbiased way, any common DNA variants throughout the genome for which the genotype is associated with a specific clinical trait or disease of interest, with the use of a statistical significance threshold accounting for the testing of hundreds of thousands of DNA variants (typically $P<5\times10^{-8}$). The first GWASs for phenotypes of relevance to cardiovascular medicine—cardiac repolarization, blood lipid levels, and coronary artery disease—were reported in 2006 and 2007[9–13] and were followed in the ensuing years by the reporting of GWASs for numerous cardiovascular traits and diseases.[14]

Two considerations have made it imperative to recruit large study populations, often numbering >100 000 individuals, to perform these GWASs. First, common DNA variants by their nature typically make only small contributions to clinical phenotypes; that is, they have small effect sizes. Second, the testing of hundreds of thousands of common DNA variants in a GWAS mandates an extremely conservative statistical

significance threshold. Thus, large study cohorts are needed to have adequate power to detect the sought-for variant-phenotype associations. This requirement has resulted in the genesis of large, multi-institutional consortia often spanning continents, even for the study of relatively common diseases such as ischemic stroke, coronary artery disease, and type 2 diabetes mellitus. This trend is evident in the example of blood lipid traits, for which studies from increasingly larger collaborations were successively published in 2007, 2008, 2009, 2010, and 2013.[10,15–19] (Association studies performed for many other cardiovascular traits and diseases are too numerous to describe here, hence the focus on the example of blood lipids.) Therefore, it is now uncommon for a publishable GWAS (ie, reporting novel findings) to be performed entirely within 1 institution or healthcare system, with the exception of some niche phenotypes.

On the one hand, GWASs have been successful in identifying large numbers of novel genomic loci harboring DNA variants associated with clinical traits and diseases (eg, 157 loci for blood lipid traits),[19] greatly advancing the understanding of the genetic architecture of the phenotypes. On the other hand, the small effect size of common DNA variants, especially those associated with a heterogeneously presenting disease, has meant that each DNA variant has relatively limited utility when its genotype is used as a predictive risk marker for the disease, usually signifying <10% change in risk per variant allele. (Of note, this does not mean that a gene affected by a common DNA variant is of minor importance to disease because the variant might have only a small effect on the function of that gene.) Even when disease-associated DNA variants are bundled together into a genomic risk score, such a risk score rarely affects disease risk prediction to a large degree, comparable to rare variants responsible for mendelian disorders (several-fold increase in risk). For example, a genomic risk score comprising 50 DNA variants associated with coronary artery disease separated individuals in the top quintile versus those in the bottom quintile of the score by 1.91-fold difference in risk of incident coronary events.[20] Furthermore, DNA variants identified by GWASs tend to lie in noncoding regions of the genome, making it less clear which genes (or potentially noncoding RNAs) are involved in disease pathogenesis and how the functions of those genes are affected, compared with variants that lie directly within the coding sequences of genes.[21,22]

When the effect size of a common DNA variant identified in a GWAS is large, as was the case of a coding variant in *SLCO1B1* that was associated with up to a 17-fold increased risk of statin-induced skeletal myopathy, the study cohort size required to discover a significant association can be small (just 85 cases and 90 controls in the myopathy GWAS).[23] This type of finding in a GWAS for a cardiovascular phenotype is much more the exception than the rule.

## RARE VARIANT ASSOCIATION STUDIES

The ability to use exome sequencing, that is, next-generation DNA sequencing of all of the protein-coding sequences in the genome, to discover genetic causes of diseases was first reported in 2009[24,25] and applied to traits relevant to cardiovascular disease in 2010.[26] The principal advantage of exome sequencing, even at the present time, is that it is substantially less expensive than sequencing of the entire genome but nonetheless is able to detect variants that are likely to be recognized as disease causing, namely those variants that directly alter the amino acid sequences of proteins. Furthermore, these coding variants are the easiest to be linked to a function and often have larger effect sizes.

Because exome sequencing in principle directly interrogates every nucleotide within the coding sequence of each gene, it is able to identify rare DNA variants, defined here as DNA variants with minor allele frequencies <1% in a given population and possibly unique to a single individual, that have not previously been cataloged. After a sufficient number of exomes had been sequenced, rare DNA variants that had been observed multiple times in the population were included on exome chip genotyping arrays.[27] They allow direct genotyping of known rare variants at significantly reduced cost compared with exome sequencing, which has permitted the study of hundreds of thousands more individuals than would have been feasible with exome or genome sequencing alone, given the current pricing of exome sequencing. Many of the studies described in the following paragraphs implemented exome chip genotyping as part of the study design.

Despite the expense of exome sequencing and, to a greater degree, genome sequencing, the potential gain from studying the effects of rare and even unique coding and noncoding variation on cardiovascular phenotypes has instigated large-scale sequencing efforts. One notable example is the Whole-Genome Sequencing Project of the Trans-Omics for Precision Medicine program funded by the US National Heart, Lung, and Blood Institute, which has the goal of ultimately sequencing >120 000 individuals, including those with cardiovascular, lung, blood, sleep, and metabolic disorders. The US National Human Genome Research Institute is also contributing to genome sequencing of large numbers of individuals with diseases such as early-onset heart disease, hemorrhagic stroke, and hypertension through funding of Centers for Common Disease Genomics. Other large programs such as the UK Biobank Initiative and the Million Veteran Program (see Role of Healthcare Institutions in Genomic Medicine section), are also undertaking large-scale exome and genome sequencing efforts.

The design of rare variant association studies (RVASs) is somewhat different from that of GWASs. Although an RVAS can be performed in the same way—interrogate each single rare DNA variant for association with a clinical phenotype—the variant is by definition uncommon in the population, so the power to detect a statistically significant association might be limited, even with data from tens of thousands of individuals available. This is true even though a single rare DNA variant can make a large contribution to a clinical phenotype, that is, a large effect size, in contrast to common DNA variants that are usually constrained with respect to their effect sizes by selection pressure in the population. Extremely rare variants with large effects merge into mendelian diseases, in which 1 variant might cause a phenotype throughout an extended family; in such cases, classic family-based techniques such as linkage studies might be more informative than the RVAS approach.

Not surprisingly, the most successful GWAS-style RVASs have identified not truly rare variants associated with disease (much less than 1% frequency) but rather low-frequency DNA variants (frequency of a few percent, intermediate between rare and common variants).[28–30] Accordingly, RVASs are usually framed as a series of "burden tests" in which each individual gene is interrogated as to whether the total number of occurrences of rare DNA variants in the gene in the cases (individuals with disease) is significantly different from the number of occurrences in the controls (individuals without disease). Such gene-level analyses can be sharpened by including only the variants that are highly likely to represent a loss of gene function (ie, nonsense, frameshift, and splice-site variants) and excluding likely benign variants (ie, synonymous variants) or variants of uncertain significance (ie, most missense variants). Functional assays combined with deep mutational scanning that can attribute phenotype-relevant quantitative metrics for every variant in a gene have been used successfully to improve the resolution of RVASs in some genes and might be generalizable.[31–33] Even so, the yield of RVASs to date has been relatively limited compared to GWASs as a result of the relatively lower power of the former compared with the latter. This limitation of RVASs has led some investigators to select individual candidate genes for analysis rather than taking an unbiased genome-wide approach, which demands a more rigorous standard for statistical significance. RVASs have been successful in identifying genes linked to coronary artery disease, including *LDLR*, *APOA5*, *APOC3*, *NPC1L1*, *ANGPTL3*, *ANGPTL4*, *LPL*, *SVEP1*, and *ASGR1*. Although most of these were previously known lipid genes, the last 2 represent novel genes.[34–42]

## PHENOME-WIDE ASSOCIATION STUDIES

The success of GWASs and RVASs notwithstanding, they suffer from a significant limitation: They are phenotype-first study designs, which means they are constrained to a single phenotype of interest. Therefore, they depend on the recruitment of a large number of individuals who are well studied with respect to that single phenotype. In the years soon after the completion of the Human Genome Project, this was not the most serious obstacle to progress. The expense of whole-genome genotyping and, subsequently, exome and genome sequencing made them the limiting factor for genomic studies of common diseases. Now more than a decade later, the tide is turning. With genome sequencing in the process of falling to less than US $1000 per individual (and exome sequencing falling to only a few hundred dollars) and the fixed nature of the genome meaning that sequencing needs to be performed only once during an individual's lifetime, the cost of sequencing has fallen to a price comparable to (or cheaper than) many routine laboratory tests, imaging studies, and other patient studies. The trend will only continue, with genotyping becoming increasingly less expensive than phenotyping, to the point that it is not inconceivable that people who interact with a hospital or healthcare system might routinely undergo sequencing.

In such circumstances, it becomes feasible to undertake genotype-first studies, to aggregate individuals with a particular DNA variant or variants and assess, in an unbiased way, whether they are associated with any of a myriad of clinical phenotypes at an appropriate statistical significance threshold that accounts for the number of phenotypes tested. Known by such labels as the reverse GWAS or the phenome-wide association study (PheWAS), this study design addresses the genetic architecture of disease in a manner distinct from and complementary to GWASs and RVASs.[43,44] It requires that a broad distribution of phenotypes be available for the entire study population so that all of the phenotypes can be interrogated simultaneously. In general, the most readily available source of a large number of clinical phenotypes is an EHR. Therefore, most PheWASs performed to date have taken place within academic medical centers or community healthcare systems that use EHRs. Furthermore, a critical element of enabling PheWAS analyses with EHRs is a bioinformatics framework that can meaningfully translate elements of the medical record (diagnosis codes, test results, descriptions in the provider notes, etc) into coherent and consistent clinical phenotypes. Ideally, the framework can operate with minimal manual curation or intervention once it has been established.

The first PheWAS analysis was reported in 2010, performed within the Vanderbilt University biobank

(known as BioVU) using genotype data from 6000 individuals and ≈500 *International Classification of Diseases, Ninth Revision* code groups abstracted from the EHR to serve as clinical phenotypes.[43] This study was notable in that it rediscovered a known association between the common DNA variant rs3135388 and multiple sclerosis using a multiple testing–corrected $P<1.0\times10^{-4}$ statistical significance threshold, despite the relatively limited sample size and the fact that the methodology for converting EHR data into phenotype data was untested. A subsequent study paired the GWAS and PheWAS approaches using data from individuals at 5 sites in the Electronic Medical Records and Genomics Network (which included BioVU). The initial GWAS analysis found that variants in the *SCN5A* and *SCN10A* loci were associated with electrocardiographic QRS duration, and the subsequent PheWAS analyses on the 2 variants found that they were associated with cardiac arrhythmias and, in the case of the *SCN10A* variant, atrial fibrillation.[45] These results emphasize the potential for PheWAS analyses using EHR data to establish pleiotropic effects on clinical phenotypes by individual DNA variants, the intrinsic limitation presented by inaccuracies of *International Classification of Diseases, Ninth Revision* codes in the EHR notwithstanding.[46]

DiscovEHR, a collaboration between the Geisinger Health System in central and northeastern Pennsylvania and the Regeneron Genetics Center, represents a partnership between a community healthcare system and a pharmaceutical company. More than 50 000 individuals with clinical phenotypes available via the Geisinger Health System EHR underwent exome sequencing, allowing the most comprehensive single-system RVAS and PheWAS analyses to date. The investigators identified a number of associations between gene variants and quantitative clinical traits that met stringent statistical significance thresholds, for example, between *EGLN1* variants and hematocrit/hemoglobin levels.[47] They also replicated a large number of known associations between lipid-related genes and blood lipid traits; in 1 notable example, they found that loss-of-function variants in *APOB* were associated with decreased low-density lipoprotein cholesterol levels and triglyceride levels but also increased alanine and aspartate aminotransferase levels, consistent with hepatocyte injury. Notably, patients receiving the *APOB*-targeting medication mipomersen experience lower low-density lipoprotein cholesterol levels and, in some cases, elevated hepatic transaminases or other liver conditions such as steatosis. This highlights the ability of RVAS/PheWAS analyses to predict both therapeutic and adverse consequences of certain genetics-guided medications.

## OTHER TYPES OF ASSOCIATION STUDIES

Besides DNA sequence data, all other types of genomic data are amenable to association analyses with clinical phenotypes and thus could in principle be used for the purposes of risk prediction, diagnosis, and prognosis. This topic has recently been reviewed in an American Heart Association scientific statement,[2] so we present only a few examples here. Epigenome-wide association studies take advantage of chips that can determine the methylation status of hundreds of thousands of potential methylation sites, called CpG sites, across the genome all at once. This makes it possible to determine which methylation sites are associated with clinical traits and diseases in an unbiased way. A recent epigenome-wide association study on blood lipid traits performed with DNA samples from peripheral blood cells identified a number of associations, with the most intriguing finding being that methylation of a CpG site near the *ABCG1* gene was correlated with decreased expression of the gene, a known regulator of macrophage cholesterol efflux and reverse cholesterol transport; increased triglycerides and decreased high-density lipoprotein cholesterol; and substantially increased risk of coronary artery disease.[48]

Transcriptomic analyses of peripheral blood mononuclear cells from patients with and without coronary artery disease with whole-genome arrays identified genes that were differentially expressed between the 2 patient groups, and subsequent analysis of the genes in replication cohorts identified a subset of 23 genes that, when measured by quantitative reverse transcriptase-polymerase chain reaction with peripheral venous blood samples, could together help identify nondiabetic patients with a high likelihood of obstructive coronary artery disease.[49,50] A genomic assay comprising the expression of the 23 genes has been prospectively assessed and validated and is now available as a clinical diagnostic test.[51,52] In a similar fashion, transcriptomic analyses of peripheral blood mononuclear cells from post–cardiac transplantation patients with or without graft rejection identified differentially expressed genes, culminating in a subset of 11 genes that, when assessed by quantitative reverse transcriptase-polymerase chain reaction with peripheral venous blood samples, could together discriminate between moderate/severe rejection and lack of rejection.[53] On validation in a randomized noninferiority clinical trial comparing it against routine endomyocardial biopsies, a genomic profile comprising the expression of the 11 genes is now available as a clinical diagnostic test.[54]

Different types of genomic studies can also be integrated to better understand heterogeneity of disease processes from a systems biology perspective, and there are now several examples of multi-omic data set analy-

ses that have identified disease-causal networks.[55] As the field advances, genomic context and network-based interactions will be key to understanding genome-phenome relationships.[56–58]

# FUNCTIONAL GENOMIC STUDIES

## Traditional Model Systems

All of the aforementioned study designs seek associations between genomic data and clinical phenotypes. They are not intended to establish causal relationships between specific molecular variations and the traits or diseases with which they are associated, but rather to generate hypotheses about causal factors for the phenotypes. Confirmatory evidence for causal relationships is typically sought in experimental model systems, usually in basic science laboratories. Ideally, one makes a specific alteration at the genetic or genomic level such as knocking out or overexpressing a gene, changing an individual DNA variant, or modifying the epigenetic status of a locus and demonstrates the predicted change in the relevant phenotype. A wide variety of model organisms are used for this purpose—ranging from yeast to fruit flies to worms to fish to mammals, most prominently *Mus musculus*, the house mouse—and in many cases have proven to be revelatory with respect to causal factors for phenotypes. Nonetheless, these organisms suffer from substantial limitations with respect to human clinical phenotypes. Particularly for complex cardiovascular diseases such as myocardial infarction, stroke, and structural heart disease, even mammalian models such as the mouse do not faithfully recapitulate all aspects of human pathophysiology (eg, coronary artery disease, some aspects of lipoprotein metabolism). With respect to genomic studies, another severe limitation is that noncoding portions of the genome, which are increasingly understood to be critical for the regulation of gene activity, are poorly conserved across species. This complicates efforts to understand how noncoding genetic variation discovered in human studies influences human clinical phenotypes.

Human-centered functional genomic studies can in principle be performed with primary human tissues. Although some cell types are relatively straightforward to obtain from living patients, maintain in culture for some time, and even genetically modify in culture (eg, peripheral blood mononuclear cells and hematopoietic stem cells, modified with the use of viral vectors or transfection reagents), other cell types of relevance to cardiovascular traits and diseases are not so accessible (eg, cardiomyocytes, hepatocytes, and vascular endothelial and smooth muscle cells). Although it is feasible to obtain some of these cell types during surgical procedures or from recently deceased cadavers, as is being done in the Gene-Tissue Expression project[59] and in the Stockholm-Tartu Atherosclerosis Reverse Network Engineering Task project,[60] these cells still suffer from the limitation that they cannot be maintained in culture long term or genetically modified. Instead, they are used for genomic association studies, for example, assessing for tissue-specific associations between DNA variants and expression levels of nearby genes (known as expression quantitative trait loci), and serve to generate hypotheses rather than test hypotheses.

## Human Induced Pluripotent Stem Cells

Human induced pluripotent stem cells (iPSCs) provide a model system that overcomes some of these limitations.[61] They harbor normal human genomes that allow faithful modeling of human genetic variation. They are pluripotent and therefore amenable to differentiation into any desired cell type, at least in principle. They are stem cells and therefore can be expanded from a single cell into billions of cells while maintaining genomic integrity and pluripotency. Each iPSC line is genetically matched to the individual from whom it was derived, without bearing all of the epigenetic alterations that might have accumulated in that individual's lifetime as a result of environmental and lifestyle factors. In a sense, the iPSC line represents the individual's baseline genetic state. Finally, iPSCs have proved to be quite pliable with respect to genetic alteration, especially with genome-editing tools such as TALENs (transcription activator-like effector nucleases) and CRISPR (clustered regularly interspaced short palindromic repeats)-CRISPR–associated 9 (Cas9).[62,63]

iPSCs can be used in at least 3 ways that are relevant to genomic medicine. First, they can be used to perform unbiased genomic association studies in a manner similar to primary tissues obtained from living individuals or postmortem. With a sufficiently large cohort of iPSC lines from genetically diverse and healthy individuals, on the order of ≥100 lines, expression quantitative trait loci studies and other type of studies can be performed in either the undifferentiated lines or the lines differentiated to a desired cell type. Several such studies have been reported and in 1 case resulted in the discovery of novel genes involved in the regulation of blood lipid levels.[64–67]

Second, iPSCs can be used for functional genomic studies that seek to establish causal relationships. Genome editing or other means can be used to introduce suspected causal DNA variants or other types of genomic alterations into wild-type iPSC lines generated from healthy individuals, followed by differentiation and phenotyping of the wild-type and modified iPSCs into the cell type of interest.[62,67] In rigorously performed experiments of this type, any phenotypic differences between the iPSCs can be attributed as a direct consequence of the genomic alteration. Alternatively, iPSC

lines can be generated from individuals with a particular disease of interest, with genomic modification used to correct the suspected causal factor in the hope that this correction results in phenotypic rescue in differentiated cells.[68,69]

Third, iPSCs can be used to study disease in a personalized fashion, that is, to understand how disease manifests in an individual patient and to identify potential approaches to alleviate the disease. A genetically matched iPSC line can be generated from the patient and differentiated into a cell type of relevance to the patient's disease. If the differentiated cells display clear phenotypes that reflect the disease process, extensive molecular profiling can be undertaken to determine the responsible pathophysiological mechanisms.[70,71] The cells can also be used for drug screens to identify molecules that can rescue the disease-related phenotypes, pointing to a possible treatment for the patient.[72] For healthy people, it might be possible to use person-specific iPSCs to prospectively assess whether they are at risk of developing a disease or having a specific response to a medication in the future.[73,74] A collection of iPSC lines could be used to examine the effect of a given mutation on different genetic backgrounds and to examine phenotypic variations of a disease within or between families, thereby helping to identify modifying variants and pathways.

Significant limitations with iPSCs are that existing differentiation protocols tend to produce immature, heterogeneous cells that are constrained to 2 dimensions in standard tissue culture dishes and thus do not faithfully recapitulate non–cell-autonomous aspects of disease pathobiology. These are being addressed by a variety of approaches, for example, studying normal developmental processes to obtain insights into how to more effectively mature the differentiated cells, adapting tissue-engineering techniques such as the fabrication of tissues on a chip or 3-dimensional organoids, and devising coculture systems that can study the interactions between multiple cell types. Despite the current limitations, substantial progress has already been made in using iPSCs to model cardiomyopathies, rhythm disorders, valvular and vascular disorders, and metabolic risk factors for coronary artery disease and stroke.[61]

## DATA SHARING

The need for large sample sizes in GWASs, RVASs, PheWASs, and other genomic research studies has brought the issue of data sharing to the fore because sharing of data among investigators and consortia engaged in parallel genomic research efforts can greatly boost the yield of the efforts. The US National Institutes of Health have instituted policies mandating that investigators receiving funding must make genomic data (and other types of data) accessible to other investigators.[75] Other funding entities have instituted similar policies, and now many journals are holding investigators responsible for making the data linked to their publications readily available to other investigators. In the future, data sharing with minimal restrictions will continue to be essential for the success of interdisciplinary genomic research, although mechanisms to facilitate the sharing of deidentified patient data that traditionally have been subject to rigorous protections will need to be developed.

## ROLE OF HEALTHCARE INSTITUTIONS IN GENOMIC MEDICINE

To date, the vast majority of genomic studies have occurred within academic research frameworks. Investigators receiving substantial funding from governmental and philanthropic sources such as the US National Institutes of Health and the Wellcome Trust either recruited from longitudinal population cohorts comprising individuals in communities, regardless of health status, with a goal of assessing risk factors for incident diseases or sought out patients with a specific disease and appropriately matched healthy individuals in a case-control study design. In either case, study participants were screened with strict inclusion and exclusion criteria, were intensively studied with respect to both genomic data and the specific phenotypes of interest outside the context of their usual medical care, and, when appropriate, were regularly engaged by the investigators so as not to have missing data or to be lost to follow-up. Given the need for large numbers of individuals to enable adequately powered genomic studies, collaborative efforts spanning many institutions have become the norm, to the extent that there are now numerous well-organized consortia with formal names, logos, steering committees, working groups, and regular face-to-face meetings for investigators.

Although these frameworks have proven to be quite successful in advancing genomic research, they have several key limitations. First, they have been largely confined to well-funded academic medical centers. This might not be so disadvantageous when addressing rare diseases for which patients tend to be referred to these same academic medical centers for their tertiary and quaternary care. However, for common diseases, millions of patients in community settings, and especially in underserved areas, have yet to be tapped for study. This in part accounts for the vast majority of participants in genomic studies to date being of European descent, with other diverse ethnic groups being understudied or not studied at all.

Second, these frameworks have been motivated by and therefore have focused on select phenotypes that are reasonably common in order to acquire suf-

ficient numbers of individuals; thus, they are not well equipped to carry out genotype-first approaches. The reason is that existing collaborations and consortia have largely identified patients who have a fully developed disease phenotype rather than a partial phenotype or endophenotype. Understanding these disease-specific patterns with genotype-first approaches could have enormous implications for disease risk prediction. However, population-based sample sizes need to be very large, certainly much greater than 1 million individuals, to accrue sufficient numbers of affected individuals with even the more common conditions caused by rare variants (eg, hypertrophic cardiomyopathy at a population frequency of ≈1 in 500, for which 80% of genetic cause, when detected, is found within 2 genes) to examine gene- and variant-based hypotheses. This is especially the case with conditions such as dilated cardiomyopathy, for which the locus heterogeneity (now with several dozen genes implicated) makes extremely large sample sizes mandatory to begin to establish statistically valid gene/phenotype associations, much less to decipher the effects of specific variants within regions of a gene.

Third, these frameworks have largely stood apart from the clinical enterprise. The evaluation of patients for genomic research studies does not meaningfully inform their clinical care, nor does their usual clinical care inform the research studies. Indeed, study participants typically do not receive any information about what was learned from their genomic data. Furthermore, genomic research studies have focused largely on discovery, with little effort devoted to date to implementation of the discoveries for the benefit of patients. This contrasts greatly with clinical genetics, in which a focus on disease-specific cohorts with mendelian conditions has informed clinical care and led to the development of current genetic testing strategies, and some studies have returned relevant results to patients and families.[76]

Fourth, these frameworks are resource intensive. With research funding continuously under constraint from societal, political, and economic forces, and any allocation of funds to genomic research studies meaning less funds available for other types of research studies, it is becoming ever more important for genomic data to broadly serve as many uses as feasible, rather than being confined to just the study for which they were originally obtained. Going forward, it could be considered wasteful from the economic perspective to obtain the same genomic data for an individual twice, once for research use and again for clinical use, and to maintain separate infrastructures for research and for clinical care; ideally, the same data should be applied for both purposes. However, this does not take into account the time and effort of maintaining consent and the costs of data storage and provenance, as well as improved variant calling and other assessments that would demand periodic reanalysis of primary genomic data. Furthermore, unless clinical-grade exome sequencing is used, most clinically oriented experts now would consider a research exome insufficient to exclude rare variants in a relevant gene for a phenotype in question. Finally, the criteria for clinical genome sequence are still emerging, and efficient and inexpensive long-term storage of genomic data remains to be solved.

Some of these limitations can be addressed by recentering genomic research endeavors within hospitals and healthcare systems or, to put it another way, recentering the endeavors on patients in clinical settings. Several hospitals and healthcare systems have already engaged in pioneering efforts to recruit large numbers of patients directly within clinical settings to link patients' genomic data to the wealth of data available in EHRs, empowering both phenotype-first approaches (eg, GWASs) and genotype-first approaches (eg, PheWASs). Each of these pilot genomic research efforts has already incorporated data from more participants—tens of thousands—than long-running prospective cohort studies such as the National Heart, Lung, and Blood Institute's Framingham Heart Study and have the potential to scale up to much larger sizes—hundreds of thousands. One notable example of a privately run effort is the Kaiser Permanente Research Program on Genes, Environment, and Health, which since 2007 has been aggregating health survey information, biospecimens, and genome-wide genotype data on hundreds of thousands of individuals within its network of >3 million people in Northern California, linked with a single EHR.[77] Other private institutions such as the Mayo Clinic have leveraged the availability of DNA samples of patients seeking health care within their system not only to further research efforts but also to enhance patient care. For example, 76 pharmacogenes (genes with pharmacogenomic implications, ie, influence beneficial and adverse responses to medications) have been sequenced in 10 000 individuals, and the data are being integrated in the EHR and will be made available to healthcare providers on an as-needed basis to guide the prescription of drugs.

For some types of studies, the number of patients available within a single hospital or healthcare system might not be sufficient. One solution is to aggregate data from patients across multiple institutions. As described in the Phenome-Wide Association Studies section, the Electronic Medical Records and Genomics Network is an example of a multi-institutional collaboration (5 institutions) that has been successfully standardizing and combining EHR data and genetic data for GWAS and PheWAS analyses.[78,79] Another solution is to create a very large cohort with genetic data and clinical phenotype data. A sterling example of this is the UK Biobank Initiative, which was created explicitly

with the intent of improving the prevention, diagnosis, and treatment of a wide range of serious illnesses, including cardiovascular diseases and stroke, by assembling a large, longitudinal data set of genotype, phenotype, and outcomes data that are freely available to any interested investigators via an open-access model. The UK Biobank recruited 500 000 participants from the general population via the UK National Health Services between 2006 and 2010; has generated genome-wide genotype data from all of these participants; has collected blood, urine, and saliva samples; and has undertaken extensive surveying and phenotyping of the individuals on a continuing basis, although most of these data are being stored separately from the EHR and are not being made available to the participants and their healthcare providers. However, a potential advantage of the UK Biobank is the ability to link to patient data via the centralized National Health Service EHR.[80] The UK Biobank has already demonstrated its value to the biomedical research community by contributing data to numerous studies, with that impact certain to be intensified as increasingly more data are made available to investigators.

The United States has a major disadvantage in that its healthcare delivery is heavily fractured and its institutions use a diversity of EHRs, which prevents easy data aggregation. Participants in healthcare plans change providers and systems frequently, making the accumulation of longitudinal data problematic. Moreover, US healthcare institutions have generally struggled with disease prevention and health promotion, with profit incentives skewing clinical practice toward the treatment of disease. These attributes make it very challenging in the United States to leverage phenomic or genomic data outside of individual healthcare institutions without an outsize infusion of research funding. In recognition of this, the US government is investing heavily in the Million Veteran Program and, as has been widely publicized, the nascent Precision Medicine Initiative Cohort Program, also known as the All of Us Research Program. The Million Veteran Program, which is linked to the largest single health provider organization in the United States, the Department of Veterans Affairs healthcare network, has already recruited >600 000 participants and is similar to the UK Biobank in that genotype data are linked to phenotype data available via a centralized EHR.[81] A notable advantage of the Million Veteran Program is the substantial proportion of underrepresented minorities, including black and Hispanic American populations, although a disadvantage is that it is heavily skewed to male participants. The All of Us Research Program, which aims to ultimately recruit >1 million diverse participants from across the United States, is still taking shape but aspires to be the most comprehensive study of its kind.

An important consideration is that the success of genotype-first approaches in healthcare institutions depends on the quality of the patient data, particularly the data entered into and extracted from EHRs. Although the early successes with GWASs and PheWASs performed in leading-edge healthcare institutions indicate that current practices are of sufficient quality and consistency to undertake productive analyses, it is clear from studies of data entry in EHRs[82] and studies of the ability to accurately extract patient diagnoses (or lack thereof) from EHRs[83] that there is significant room for improvement. Further investigation into best practices for data entry and extraction that can be applied widely across healthcare institutions engaged in genomic research will undoubtedly improve the yield of their endeavors.

## CONSIDERATIONS FOR PATIENT-CENTERED RESEARCH

### Big Data

As described in the Role of Healthcare Institutions in Genomic Medicine section, an initial wave of genomic research studies has advanced our knowledge of the complex mechanisms of diverse biological processes while also raising awareness that a vast amount of data remain to be harnessed to improve health and to prevent disease. Ample opportunities for more widespread use of "big data" in research and clinical practice are being recognized. However, genomic research efforts can create uncertainty for healthcare professionals, patients, and families.[84] Approaches that are built on a partnership that brings together the expertise of researchers and clinicians with the trust of the public will be instrumental in facilitating large-scale research efforts, fostering shared governance, and shaping the future of informed consent and return-of-result processes in the evolving era of genomic medicine. Addressing these issues, patient privacy and confidentiality, and education of diverse healthcare teams, patients and families, the public, and policymakers will be essential to ensuring that genomic medicine becomes a reality.[85–87]

The US National Institutes of Health Big Data to Knowledge initiative[88] and the National Patient-Centered Clinical Research Network[89,90] are examples of existing big-data efforts that include both patient-driven research networks and the evaluation of potential clinical applications. These and other big-data research platforms are intended to address comparative effectiveness, safety, variations in care delivery, medication adherence, and factors driving readmissions.[91] Thus, they provide models of patient-centered research that can be emulated in the furtherance of genomic research to improve cardiovascular care.

## Shared Governance and Equity

The US National Institutes of Health recently completed a public opinion survey about participation in the Precision Medicine Initiative's national cohort study of genes and environment.[92] Seventy-nine percent of respondents reported that the study should be undertaken, and more than half of the respondents would either "definitely or probably participate in a study if asked."[92] Opinions on the study and willingness to participate increased with education level and decreased with age; however, there were no significant differences between racial/ethnic groups for these questions. Another interesting aspect of this survey was that 71% of respondents agreed that researchers and participants should be equal partners in the study development and, specifically, the selection of the kinds of research questions to be answered with the cohort and sharing in the decision making of how the results should be disseminated. These findings are consistent with other research studies showing that individuals place a high value on receiving data back from the studies in which they participate.[93]

Approaches that foster transparency, work to eliminate disparities, and promote health equity will be essential in improving population health. The directors of the Centers for Population and Health Disparities have created a model that focuses on social approaches needed to achieve health equity, in which they note that bridging knowledge gaps in achieving healthcare equity requires understanding how quality improvement and patient-centeredness can inform equity initiatives, inform practice and policy, and enhance communication and cultural competency among health professionals to minimize the potential risks of population-based genomic investigations.[94,95]

## Informed Consent

Informed consent is key to both research and clinical activities, but it poses new challenges in the era of genomic medicine. For example, whether to return incidental findings is a topic of extensive and continuing debate, especially if the findings have pharmacogenomic implications that could directly affect future medication choices or might signify future risk of mendelian disorders.[96–98] Other important issues related to the informed consent process are the amount of technical detail to include in the informed consent process so that patients with varying degrees of genomic literacy are truly informed,[99] the appropriate use of new and innovative digital formats to obtain informed consent,[100] the inability to reliably interpret many of the findings that will be discovered with genomic testing, and tempering participants' expectations that genomics-based tests will translate into immediate, meaningful improvements in their clinical care. Innovative models for obtaining informed consent such as patient-centered consents, the use of mobile and web-based platforms, and "tiered" and "binned" approaches for future use in multiplex testing[101] are currently under development and highlight that informed consent is itself an area of active investigation.

Approaches that would allow patients to give broad consent for future studies or to "opt in to" or "opt out of" certain types of genomic tests at certain time points over their lifetimes need to be developed. Currently, most informed consents are not dynamic and do not have time triggers or automatic flags in place for re-evaluation. As genomic medicine approaches evolve and the public becomes more engaged, there will be a greater need for dynamic informed consent processes that change in relationship to the individual's needs. For example, a young adult with a family history of hypertrophic cardiomyopathy might agree to enroll in a biobank but initially opt out of genetic testing and decide on an approach that involves clinical monitoring with ECGs and echocardiograms, but perhaps a decade or more later, that individual may opt in for genetic testing and preimplantation counseling before starting a family while still retaining the flexibility to choose whether to make the data available for research studies at any time. Dynamic informed consent processes that reflect the rapid advances and application of genomic medicine need to be seamlessly integrated with the changes one can expect in an individual's health choices during the lifetime.

## Creating a Social Contract of Trust

One approach to addressing these various issues might include the creation of a task force of providers, patient advocates, policymakers, and other stakeholders to evaluate the "genomic best practices" related to informed consent, privacy, and confidentiality. Another approach might include developing partnerships with underserved and underrepresented minority communities and advocacy groups to develop trust and transparency around genomic medicine research collaborations. It has been shown that an approach that actively engages community and advocacy groups and seeks to design studies that are attractive to patients helps to publicize the projects, recruit participants, and support funding efforts.[102]

## Education of the Public and Healthcare Providers

Members of the healthcare workforce, patients, families, and the public will need to have sufficient genomic literacy to make use of genomic information that affects decisions related to their life health choices. This creates the need for a new approach to genomics education

that takes into account the widely varying degrees of genomic literacy among the general public, patients, and healthcare providers and the specific needs of these groups. This might require online resources that are interactive and provide a series of general modules on a variety of health-related topics. Decision support tools for providers and patients that provide useful information will be critical in providing education about the propensity of individuals and families to develop a certain disease, information that facilitates a correct diagnosis, and guidance in the selection of the most appropriate prevention and treatment choices. Easy-to-use tools that allow up-to-date and accurate information to be available in multiple languages and to be accessed as frequently as needed will be essential to promote genomic literacy and to enhance informed shared decision making.

As proposed by recent American Heart Association scientific statements and committees of the Eurogentest project and the European Society of Human Genetics, a pragmatic solution to enhance genomic education among healthcare providers is the establishment of common standards for education and clinical practice, with core competencies that could be applied across healthcare disciplines.[103–105] The core skills and knowledge needed include how to evaluate a family history and recognize potential "red flags" that might signal an individual or family to be at increased genetic risk. The continued rapid advances in genomic technology and the application to clinical practice will require that all providers possess basic knowledge in order to deliver quality care and to be able to recognize when an individual or family should be referred to specialists in genetics and genomics.

Promoting genomic literacy among patients and their families is a bigger challenge in that it would require a systematic effort to improve understanding across the entire population. Although no easy solutions will be forthcoming, the US National Human Genome Research Institute has recently launched an effort called the Genomic Literacy, Education, and Engagement Initiative,[106] which would comprehensively target 3 audiences nationwide: kindergarten through grade 16 (college) students, the general public, and healthcare providers. The resources generated by this initiative could be adapted for local use within hospitals and healthcare systems and from there disseminated throughout communities.

## PERSONNEL NEEDED FOR GENOMIC MEDICINE ENDEAVORS

As research endeavors in genomic medicine take shape via a patient-centric model, they will require teams of varied personnel with different types of expertise. Data scientists will play an increasingly large role. There is the potential to generate vast amounts of genomic data from patients. The stored version of a patient's germline genome, which can be collected just once during the lifetime, need not contain all 6.2 billion bases but can be condensed to just the variations from the reference genome, although this will still include millions of pieces of data, including quality metrics (to indicate the reliability of each called variation and whether it warrants confirmation by another technique). Although undoubtedly challenging to implement, especially in a country like the United States where healthcare delivery is highly fragmented, informatics pipelines that efficiently process the billions of sequence reads obtained in whole-genome sequencing and condense them to variations (whether single nucleotide variants, insertions-deletions, variable number tandem repeats, or copy number variants) and that interface with each patient's EHR will be mandatory. It should be recognized that consequential changes to the genome can occur during the lifetime, for example, with cancer or with clonal hematopoiesis of indeterminate potential, the latter of which is now appreciated to be a risk factor for coronary heart disease.[107] This might necessitate the processing and storage of multiple versions of a patient's "somatic" genome during the lifetime, for example, from tumor samples or blood samples obtained in older patients.

Beyond genome sequences, various types of omic data—transcriptomics, epigenomics, proteomics, metabolomics—and metagenomic data will be collected. Being highly labile, each of these types of data would probably not be obtained just once during a patient's lifetime but rather at various intervals or continuously to assess a patient's changing health over time. In contrast to the human genome, these types of omic data sets do not have a universal reference against which they can be compared, so the entire data sets would need to be processed and stored.

Data scientists will be needed not just to devise the means to process and store this wealth of genomic data as they are but also to retrieve and convert the data into formats usable by the rest of the genomics team. This is particularly relevant to EHR data, for example, extraction of data from the formats needed for clinical documentation and billing (provider notes, *International Classification of Diseases* codes, etc) and conversion into formats suitable for association analyses (well-defined phenotypes with diagnostic criteria that are standardized across institutions engaged in genomic research). Because EHR-based work will require clinical knowledge and familiarity with the conventions of clinical practice, the data scientists will need to work closely with clinical providers and clinical research staff who have this knowledge and familiarity.

Clinical research staff will play an instrumental role in recruiting patients into biobanks and other types of studies conducive to genomic research, explaining the purpose of genomic research, conveying the potential benefits (and potential harms) of participating in genomic research, and otherwise guiding patients through the consent process. They might also contribute in other ways to the infrastructure of biobanks (eg, collection, processing, and storage of blood and DNA samples).

Once data are collected and converted into forms suitable for analysis, genetic epidemiologists, system biologists, and statisticians will be crucial in designing studies that discover new relationships between genomic data and clinical phenotypes and subsequently validate these relationships. It will start with straightforward association analyses, along the lines of what has already unfolded over the past 10 years with GWAS and PheWAS analyses, and progress to increasingly complex, multidimensional analyses incorporating several levels of genomics data and permitting gene-gene, gene-environment, and other interaction analyses. These personnel will also play an important role in coordinating studies that need to be implemented across numerous institutions, that is, standardization of analysis plans.

Basic scientists will be called on to contribute to endeavors in genomic medicine. One of the major goals of genomic medicine is a better understanding of disease mechanisms, which will require basic science investigations in the laboratory with animal models or cell-based models (eg, primary human cells, iPSCs, other cultured human cell lines). It is to be hoped that some of the disease mechanisms that come to light will point to new therapeutic approaches that could benefit patients. Basic scientists will need to initiate the process of therapeutic development, whether it entails traditional drug screens or testing of genetic strategies (eg, gene therapy, genome editing, oligonucleotide-based therapies, antibody-based biologics) in preclinical models.

Finally, clinical providers, that is, physicians, genetic (genomic?) counselors, nurses, pharmacists, etc, will be instrumental in ensuring that just as genomic research studies will need to accrue patients, the patients will ultimately accrue benefits from genomic medicine. On the research side, providers will work with clinical research staff to enroll patients in biobanks and other genomics-based clinical studies and trials, as well as to submit genomic data to research databases. On the clinical side, as informative clinical genomic tests are developed (see the Translating Genomic Research Findings Into Clinical Tests section), providers will arrange for genomic testing to be performed in the appropriate circumstances, to convey the results of the tests to patients in an informative and responsible way, to choose appropriate medications and treatments in light of the results of the tests, and to otherwise translate genomic medicine into the clinic. The clinical paradigm has already been established with respect to clinical genetics programs in many hospitals and healthcare systems, and these programs will undoubtedly expand and evolve to incorporate genomic testing.

An important consideration is who will lead interdisciplinary endeavors in genomic medicine; that is, who will be the quarterbacks of the teams? This role will require a skill set that traditional MD or PhD training programs do not currently provide. We envision a new type of training opportunity for physician-scientists that will allow them to become well versed in the wide range of issues relevant to genomic medicine and to become qualified to coordinate the diverse members of the team. One mechanism would be a category of US National Institutes of Health training grants specifically geared toward genomic medicine. Supported programs would enable trainees to take coursework on the latest advances in genomic technologies as applied to human health, cellular and animal models, biomedical informatics, biostatistics, and ethical/legal/social implications of genomic medicine. They would also be able to participate in clinical rotations in which they would gain first-hand experience with topical issues such as next-generation sequencing, interpretation of sequencing data results, patient privacy and consent, and reporting of results to patients.

## TRANSLATING GENOMIC RESEARCH FINDINGS INTO CLINICAL TESTS

A major goal of interdisciplinary efforts in genomic medicine is to identify novel associations between molecular signatures, whether within the genome or within the expressed genome, and clinical phenotypes, whether responses to medications, onset of diseases, or disease outcomes, that can be leveraged for the improved diagnosis, prognosis, and treatment of patients. In this section, we address the challenges entailed in translating these novel research findings into clinical tests.

The first consideration is whether research findings from genomic studies are verifiable and generalizable across patient populations. If a finding has not been replicated in multiple independent studies of cohorts distinct from the original study cohort, it is premature to entertain clinical use of a test derived from the research finding. The publication of the US Institute of Medicine (now the National Academy of Medicine) report *Evolution of Translational Omics: Lessons Learned and the Path Forward* in 2012 was in part prompted by the clinical application of tests that lacked external validity and potentially harmed patients.[108]

One such cautionary tale centers on the *KIF6* gene, in which the Trp719Arg variant was reported to be associated with both cardiovascular risk and response to statin therapy in several initial studies.[109–113] The clinical implication of these observations was that noncarriers of the Trp719Arg variant received little benefit from statin therapy. On that basis, a company marketed a *KIF6* genotype test to determine whether individual patients should receive statin therapy, and hundreds of thousands of the tests were sold. Subsequent analyses in large prospective cohort studies demonstrated no association of the *KIF6* Trp719Arg variant with either cardiovascular risk or response to statin therapy,[114,115] and a large association study similarly found no link between the variant and cardiovascular risk.[116] It became clear that the *KIF6* genotype test had been prematurely and inappropriately introduced into clinical practice and that it likely harmed patients by persuading their providers to withhold statin therapy on the basis of the invalid premise that the patients' genotypes rendered them unresponsive to therapy.

There are multiple lessons to be drawn from examples such as the *KIF6* genotype test. First, the quality of the science underlying a proposed test must be carefully assessed before the development and implementation of the test. The validity of the test is better ensured when there is replication in multiple studies with large numbers of individuals, ideally drawn from diverse populations. Second, there should exist readily available cohorts in which an initial discovery can be rapidly tested for replication. If such replication studies cannot be quickly performed, financial incentives might prompt the premature clinical implementation of a nonvalidated test. This highlights the need for ongoing interdisciplinary efforts in genomic medicine at numerous hospitals and healthcare systems around the world, providing diverse opportunities for rapid external validation of promising discoveries.

Even if a genomic finding is demonstrated to be valid, any test that is created to take advantage of that finding will need to be shown to have clinical utility if it is to be deployed in the healthcare setting. Some considerations are whether the results of the test are clinically actionable—that is, if it will potentially alter the management of the patient—or, failing that, whether it sufficiently improves the prediction of risk, diagnosis of disease, or prognostication of disease outcomes so that the patient is better informed about her health. The judging of the clinical utility of the test with respect to prediction, diagnosis, or prognosis will entail assessment of test characteristics such as discrimination, calibration, reclassification, and cost-effectiveness.[117–119]

Discrimination is the ability of a test to separate patients who will ultimately develop a disease, who currently have the disease, or who will have a poor outcome from the disease from patients who will not. A standard metric of discrimination is the area under the receiver-operating characteristic curve, also called the C statistic, which is calculated by plotting the true-positive rate of the test (sensitivity) against the false-positive rate (inverse of specificity).[120] Put another way, the C statistic is a measure of the probability that a randomly chosen person from the disease group has a higher risk than a randomly chosen person from the nondisease group. The ideal test has a C statistic of 1, whereas a test with no ability to discriminate has a C statistic of 0.5. The commonly used Framingham Risk Score for coronary heart disease risk has a C statistic of ≈0.75,[121] which signifies some ability to discriminate but with substantial room for improvement.

Calibration is the degree to which the predicted risk probabilities of a test for various subgroups of patients (with differing levels of risk) match their observed risk proportions. One commonly used means to assess calibration is the Hosmer-Lemeshow test,[122] which divides a population into 10 subgroups based on predicted risk (deciles). In general, calibration is more important for tests that forecast future risk (prediction and prognosis) than for tests that determine whether a patient currently has a disease (diagnosis), whereas discrimination is important for all tests.

Reclassification metrics are useful to assess the extent to which a test administered to a group of patients will result in a change in clinical management for any of the patients. One commonly used metric, the net reclassification index,[123] signifies the proportion of people for whom the predicted level of risk is changed by the test (eg, from low risk to intermediate risk or from intermediate risk to high risk). Tests are felt to be more clinically useful if the net reclassification index is high and the management of patients is quite distinct for different risk groups. For example, it is particularly helpful when it is possible to reclassify intermediate-risk patients who are "on the fence" with respect to a treatment to either a lower-risk group or higher-risk group for whom the treatment strategy is more certain.

Arguably the most important characteristic of a proposed test from the perspective of a healthcare system is the cost-effectiveness of the test. The number of individuals who need to undergo the test in order to correctly predict, diagnose, or prognosticate 1 additional event is an important metric in this regard. The higher the number needed to test is, the higher the cost associated with the benefit gained from each desired event is. Other considerations besides the cost are the inconvenience and potential for outright harm associated with the test itself, as well as the long-term negative consequences to patients of false-positive or false-negative results of the test.

Traditionally, determination of test characteristics occurs in large research cohorts that do not necessarily match well with real-world conditions. For exam-

ple, the Framingham Risk Score that was developed through analysis of the National Heart, Lung, and Blood Institute's Framingham Heart Study cohort has well-known shortcomings, especially when applied to women and to patients not of European ancestry.[124] The 2013 American College of Cardiology/American Heart Association guideline on the assessment of cardiovascular risk introduced the Pooled Cohort Equations with the goal of incrementally improving on the Framingham Risk Score; they share most of the components of the Framingham Risk Score but were calibrated to a wider age range and a more diverse population that included African Americans.[125] Despite these improvements, the Pooled Cohort Equations were subsequently found to overestimate risk in a variety of population cohorts.[126] Neither the Framingham Risk Score nor the Pooled Cohort Equations include family information or genomic data, suggesting that the incorporation of genomic data has the potential for additional incremental improvement of risk prediction.

Ideally, test characteristics should be assessed in numerous, diverse populations. The existence of a large number of readily available cohorts within hospitals and healthcare systems would permit the rapid assessment of a genomics-based test with respect to discrimination, calibration, and reclassification. Furthermore, cost-effectiveness calculations would be expedited if they could be modeled directly within hospitals and healthcare systems, where a more accurate accounting of costs, numbers needed to test, and total numbers of patients who could potentially benefit (and potentially be harmed) can occur. If a proposed test were modeled and ascertained to perform favorably in many institutions, it would provide a strong impetus for adoption of the test in clinical practice.

The final consideration is implementation of a test. In the current environment, the implementation of a new test tends to be very slow. This is in part a result of the need to satisfy regulatory standards set forth by authorities such as the US Food and Drug Administration and Centers for Medicare & Medicaid Services. In the future, the ability to marshal evidence in support of a test in many hospitals and healthcare systems rapidly, rather than over the course of many years as tends to be the case nowadays, should accelerate regulatory approval. A major barrier to implementation is the ability to successfully demonstrate that the use of a test and resultant treatment decisions can alter clinical outcomes of patients compared with the current standard of care. A means by which this can be accomplished is to undertake genotype- or biomarker-based clinical trials, which can be expensive and difficult to perform[127] but could be expedited by the involvement of institutions already actively engaged in genomic medicine efforts.

Two clinical trials of warfarin pharmacogenomic testing strategies have demonstrated the feasibility of performing randomized clinical trials to establish the superiority of approaches that exploit genomic information. The EU-PACT trial (European Pharmacogenetics of Anticoagulant Therapy) found that patients with atrial fibrillation or venous thromboembolism in whom a point-of-care test for the *VKORC1* and *CYP2C9* genotypes related to warfarin metabolism was performed and was used to guide initial warfarin dosing experienced a higher percentage of time in the therapeutic international normalized ratio range, fewer episodes of excessive anticoagulation, and decreased time to reach a therapeutic international normalized ratio compared with patients whose initial warfarin dosing was managed by routine clinical practice.[128] The more recent GIFT trial (Genetic Informatics Trial) of Warfarin to Prevent Deep Vein Thrombosis assessed the use of *VKORC1*, *CYP2C9*, and *CYP4F2* genotypes for initial warfarin dosing in the setting of venous thromboembolism prophylaxis for hip and knee arthroplasty and found that patients with genotype-guided management had a 3.9% absolute reduction (27% relative reduction) in the combined risk of major bleeding, an international normalized ratio of ≥4, venous thromboembolism, or death within 30 days compared with patients with routine clinical management.[129] More clinical trials of this kind should be pursued, arguably not just for genomics-based tests but for all types of laboratory tests.

Another barrier to implementation is the reluctance of individual providers to incorporate a new test into their practice, at least until many of their peers are doing the same, and in turn the reluctance of payers to provide reimbursement for testing. In the future, the central role of hospitals and healthcare systems in the development and validation of genomics-based tests should facilitate the rapid implementation of the tests across those same institutions, all at once, and help to overcome the reluctance of providers and payers.

## CONCLUDING REMARKS

We envision that genomics will play an important role in shifting clinical care away from its current focus on being reactive (treating disease that has already manifested) to being proactive (preventing disease before it fully manifests) (Figure). This mandates that genomic testing be done early, ideally long before a patient is sick, perhaps in some cases as early as birth. It is possible that within 2 decades many patients will be routinely undergoing different types of genomic testing at costs that are comparable to the costs of standard laboratory tests. Some types of data such

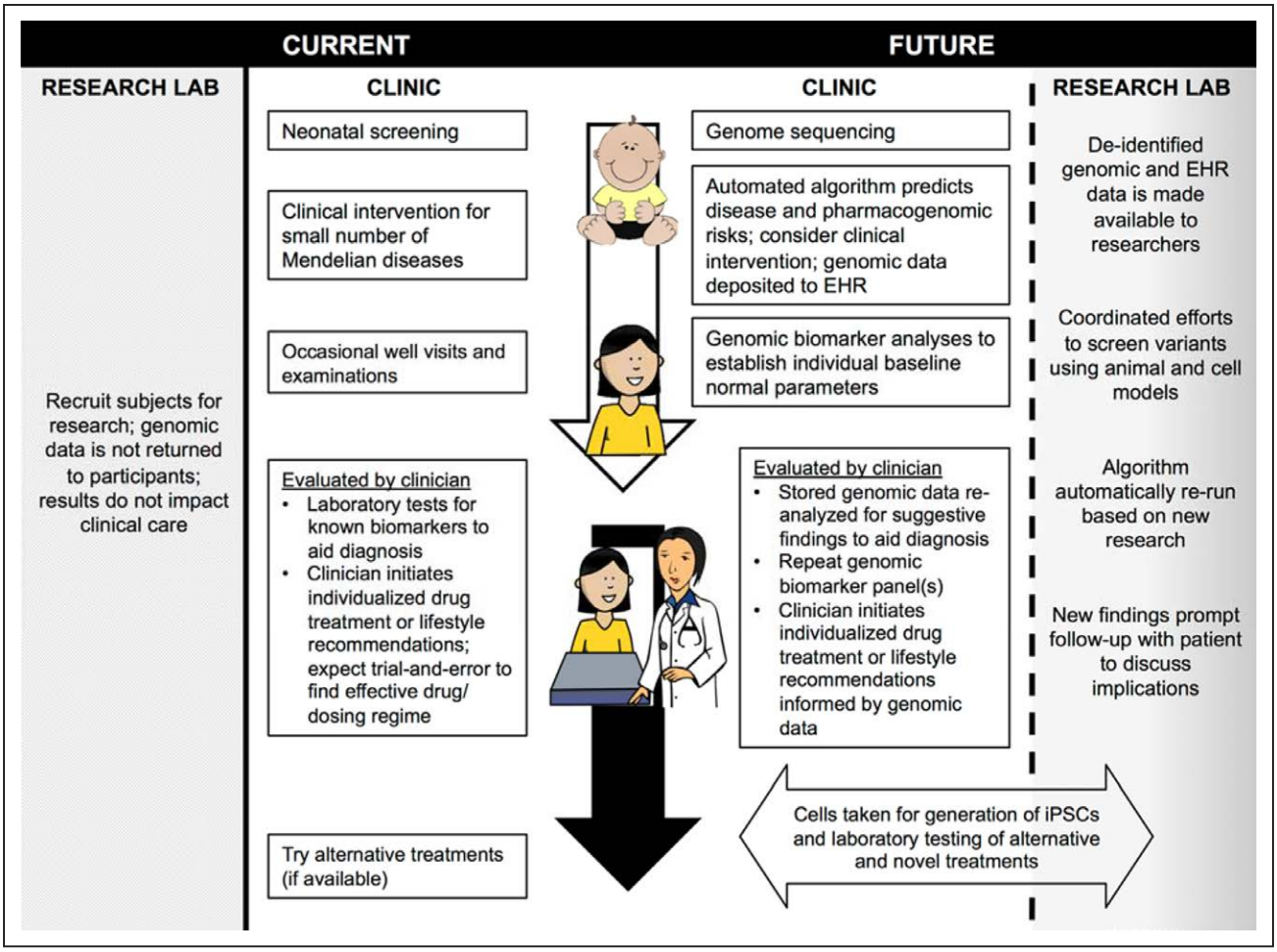


**Figure. A vision of genomic medicine in the future.**
EHR indicates electronic health record; and iPSC, induced pluripotent stem cell.

as DNA variants that have pharmacogenomic implications would be routinely integrated into the EHR for all patients.

As noted, whereas a person's germline genome is stable throughout the lifetime, the expressed genome is quite labile. Plasma proteomic and metabolomic profiles would be assessed at a certain age, when patients are still healthy, to provide a baseline against which to compare when the patient is older or has incipient illness. The gut microbiome might also be assessed at the same time. Patients would undergo periodic metabolic and fitness testing, for example, with wearable devices for weeklong intervals to assess heart rate, activity, sleep quality, glucose levels, and diet. These data would be analyzed by an automated system to flag anything that warrants immediate follow-up. Physicians, genomic counselors, nurses, pharmacists, and other healthcare providers who are appropriately educated with respect to the interpretation of these data would routinely draw on the data to offer recommendations about disease risk, lifestyle changes, and medication choices to prevent at-risk patients from developing diseases or, failing that, to improve disease outcomes.

There would still be an important role for reactive point-of-care genomic testing in certain situations, for example, patients in the throes of acute coronary syndromes and patients who have recently undergone cardiac transplantation, in order to more accurately prognosticate patient outcomes and to choose the optimal therapeutic approach to address the immediate needs of each patient.

Ideally, these genomic data would be integrated into the EHR for many patients, and for those patients who have opted in, the data would be accessible to researchers for use in genomic studies for both the investigation of the root causes of diseases and the identification of molecular profiles that predict disease risk. In the long term, the studies performed by these researchers will yield novel insights into disease and improved methods to use the patients' genomic data for the prediction, prevention, diagnosis, prognosis, and treatment of those patients and ultimately pave the way for improved cardiovascular and stroke care for the entire population.

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The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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# Interdisciplinary Models for Research and Clinical Endeavors in Genomic Medicine: A Scientific Statement From the American Heart Association

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On behalf of the American Heart Association Council on Genomic and Precision Medicine; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Radiology and Intervention; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council

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