THE PROMISE OF PRECISION MEDICINE FOR CARDIOVASCULAR DISEASE & THE POTENTIAL IMPACT ON CLINICAL TRIALS

This article reviews the role of precision medicine in the diagnosis, prevention, and treatment of cardiovascular disease and comments on the potential of precision medicine strategies in cardiovascular clinical trials.

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During his 2015 State of the Union Address, President Obama formally launched the Precision Medicine Initiative (PMI), which called for $215 million in federal funding for medical research to develop a patient-tailored integrative approach to disease prevention and treatment.

"I want the country that eliminated polio and mapped the human genome to lead a new era of medicine – one that delivers the right treatment at the right time," spoke President Obama.

By ushering this new era of precision medicine, President Obama in effect recognized the many years of groundbreaking research dedicated to the identification of the genetic causes of diseases and the development of targeted therapeutics such as the inherited rare disease, cystic fibrosis, where precision medicine is being used not only for drug development but also to predict individual patient responses to such therapies. Indeed, the mission statement of the PMI is "to enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward the development of individualized care." Buoyed by the support of government and private funding, considerable progress has been achieved in the application of precision medicine to the prevention and treatment of diseases, most notably, oncology. While the short-term goals of the PMI centered on development of new therapies in oncology, the long-term goals extend to all areas in health and healthcare. Consequently, the application of precision medicine in other complex disease processes, such as cardiovascular disease, has gained burgeoning momentum with increased financial support and a widely-accepted scientific rationale. Indeed, the American Heart Association introduced its Precision Medicine Platform in 2017 which allows researchers and physicians to analyze big data in cardiovascular disease databanks and registries from leading academic research centers in the US.

Data analysis and deep clinical and molecular phenotyping underscore the limitations of conventional approaches to disease.

DEFINING PRECISION MEDICINE

The term "precision medicine" has evolved over the last decade. What was once broadly considered "the right treatment to the right patient at the right time," has evolved into an analytical and integrative approach to disease prediction, prevention, diagnosis, and tailored treatment by incorporating individual genetics, lifestyles, environmental exposures, and experiential variability. The precision medicine strategy has achieved the most notable success in the field of hematology/oncology, where patient's tumors are molecularly analyzed to create bespoke therapies, e.g., chimeric antigen receptor T (CAR T) cell therapy. Recent advances in the field of "omics" (e.g., genomics, transcriptomics, epigenomics, metabolomics, and proteomics), and other technologies that provide data

analysis and deep clinical and molecular phenotyping underscore the limitations of the conventional approach to disease. Perhaps, the most direct way to begin to define precision medicine is to highlight what precision medicine is not.

The traditional western system of medicine is based on a reductionist approach, which uses a multilevel system with inputs from the patients, the physician, and the medical system using evidence-based practice. For example, the first level involves the assessment of the patient's symptoms as a change from baseline. Evaluation by a physician or care provider produces a personalized assessment of the physical signs and symptoms of a disease process, usually leading to evidence-based therapies. While this reductionist approach can treat symptoms and lead to disease improvement and cure in some disease processes, this conventional approach is not always successful, especially in the setting of complex illness, like cardiovascular diseases which have multiple etiologic factors of pathogenesis. Indeed, often too little attention is given to individual variance in etiology and pathophysiology. Reductionist medicine ignores the heterogeneity in disease pathophysiology and disease phenotype ("pathophenotype"), clinical presentation, and response to treatment. This "one-size-fits-all" strategy assumes that all patients with common signs and symptoms share the same pathophenotype and will respond similarly to medical therapies.

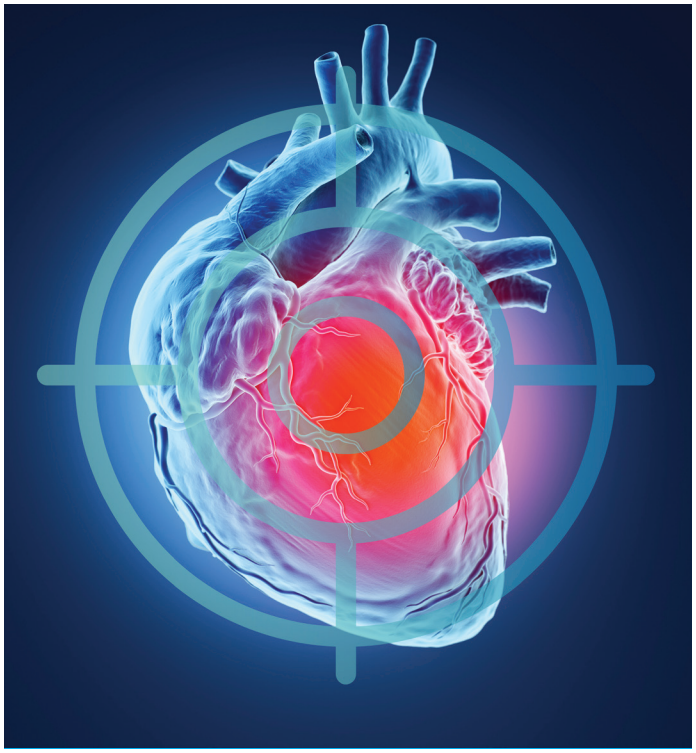
In concordance with reductionism, the treatments used to fight disease are generally supported through randomized controlled trials, in which a common phenotype is assumed, and a treatment effect is simplified to a bell-curve or Gaussian distribution with a median and standard deviation measurement, i.e., a population-based approach. Enrolled subjects are randomized based on the variable of interest, such as blood cholesterol level. One limitation of this oversimplification is that only relatively large differences are detectable as being statistically significant. Results are often expressed as an average finding per cohort, while the actual range of responses may be overlooked. An illustrative example of the weakness of this reductionist approach is the syndrome of chronic heart failure. Heart failure is clinically defined by cutoff points based on left ventricular ejection fraction, stages, or functional class. These traditional classification systems ignore the pathophenotype of individual subjects. Indeed, such deficiencies of the traditional approach to heart failure may be a leading reason for the failure of many therapeutics to achieve treatment success for this deadly disease. In support of this hypothesis, a post-hoc cluster analysis using 45 baseline clinical variable from 1,619 patients in the HF-ACTION trial, which compared exercise training with usual care in chronic systolic HF patients, revealed significant heterogeneity among patients with segregation into clusters not predicted based on initial phenotype. The authors supported the need for improved phenotyping of chronic heart failure patients.

In contrast with conventional medicine, precision medicine does not assume a common phenotype for the purpose of studying a population response. Rather, **the goal of precision medicine is to move away from population averages and medians and instead, focus on the subject's individual unique phenotype, as well as response to treatment.** This targeted approach shifts the focus to the at-risk populations at the tails of the curve. Precision medicine targets prevention and treatment while considering individual differences in genetics, exposures, lifestyles, and health factors that shape a person's pathophenotype versus a health phenotype. Establishment of the pathophenotype for a given disease lies at the core of precision medicine. Indeed, identification of the relationship between the factors that constitute a health phenotype versus a pathophenotype is a critical requisite for the success of precision medicine. Individuals who share a common biological trait, such as hypertension or hypercholesterolemia, may display different pathophenotypes at a molecular level. Advanced tools, such as pan- "omic" analysis, may result in the recognition of clusters of distinct phenotypes with different implications for disease risk, prognosis, or response to therapies. Decisions in precision medicine are based on information from multiple sources, including data from systems biology, clinical research, laboratory tests, "omic" data, imaging, and environmental exposures. Understandably, the achievement of precise phenotyping is challenging and complex, which reminds us that this approach is very much still in its infancy.

THE ROLE OF PRECISION MEDICINE IN CARDIOVASCULAR DISEASE AND CARDIOVASCULAR CLINICAL TRIALS

The definition of a disease phenotype is less well developed in cardiovascular medicine than in hematology and oncology. Traditionally, cardiovascular diseases are defined by symptoms or simple diagnostic testing. Moreover, cardiovascular diseases often develop slowly, over decades, and are often mistaken to be less serious than other conditions. Evidence-based therapies for cardiovascular disease have been primarily focused on lifestyle modifications to reduce the risk for coronary and vascular disease, such as smoking, diabetes prevention/treatment, diet, and exercise, blood pressure control, and blood cholesterol treatment. These cardiovascular risk factors are largely based on patient registries using a population-based strategy. While such lifestyle modifications have led to a modest reduction in cardiovascular adverse events and deaths (20-30% over ten years), cardiovascular disease remains the leading cause of death in the US and globally – one death occurs from cardiovascular disease every 40 seconds in the US. Current projections indicate that cardiovascular deaths before the age of 70 may increase worldwide from 5.9 million in 2013 to 7.8 million in 2025.

Thus, there is a clear unmet need for the application of precision medicine to aid in the prevention and treatment of numerous cardiovascular diseases. Current targets of precision medicine include genetically based cardiovascular diseases and cardiomyopathies, e.g., hypertrophic cardio-myopathies, dilated cardiomyopathies, amyloid transthyretin cardiomyopathies, inherited rhythm disorders, familial hyperlipidemias, and inherited connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome. Moreover, even broadly classified cardiovascular disease syndromes, such as heart failure, hypertension, coronary artery disease, and hyperlipidemia, represent potential targets for a precision phenotyping approach. In drug development, application of a precision medicine approach consists of defining distinct disease phenotypes among patients displaying a biological trait (e.g., hypertension) or categorized by a diagnostic cut-off point (e.g., left ventricular ejection fraction), identification of molecular targets, and early predictive assessment of treatment effect possibly by using surrogate biomarkers.



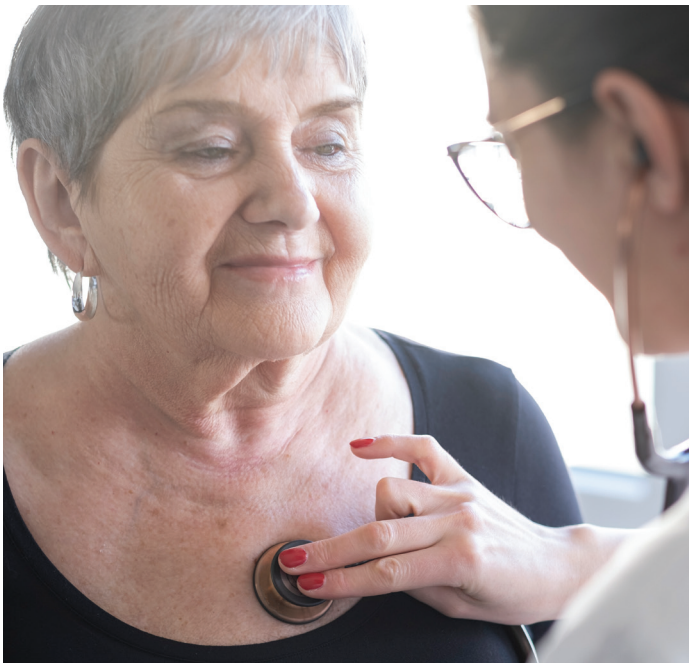
Illustrative of the potential benefit of a precision medicine approach in cardiovascular trials are the recent results of the PARAGON-HF study2. In this prospective randomized controlled trial, 4,822 patients with heart failure and an ejection fraction of 45 percent or higher were randomized to receive either sacubitril-valsartan (angiotensin receptor-neprilysin inhibitor-angiotensin receptor blockade) or valsartan. The combination drug treatment narrowly missed the primary endpoint of the lower rate of total heart failure hospitalizations and death from cardiovascular causes. However, a prespecified subgroup analysis demonstrated that there was heterogeneity in the study population of heart failure patients in terms of treatment effect. Indeed, there was a greater benefit, which was statistically significant, in patients with an ejection fraction below the median of 57%, with a 22% reduction rate, and in women, with a 28% reduction rate, in the composite endpoint of heart failure hospitalizations and cardiovascular death.

The fact that the PARAGON-HF trial narrowly missed its primary endpoint using a population-based approach to heart failure should not be entirely surprising. Accumulating evidence confirms the existence of numerous diverse subphenotypes within the heart failure with preserved ejection fraction (HFpEF; LVEF>50%) population. A "one-size-fits-all" strategy would be predicted to ignore the individual characteristics, molecular factors, environmental exposures, and sex differences found among the heterogeneous HFpEF population. Indeed, the PARAGON-HF subgroup analysis also suggests that the heart failure with borderline or midrange EF (LVEF 41-49%) may also represent a subphenotype that benefits from combination angiotensin receptor-neprilysin inhibitor and angiotensin receptor blockade.

The hope is that precision medicine will lead to a more efficient clinical research strategy for a tailored clinical therapeutic. Naturally, precision medicine leads to precision trials by targeting subgroups that are more likely to display drug effect, i.e., smaller but "smarter" over larger and "dumber" trials. In effect, precision medicine provides a scientific and large data-driven method for predictive population enrichment. For example, genomic approaches may help to improve study design in cardiovascular trials by identifying individuals with a specific risk for the development of cardiovascular disease. This approach in clinical research has obvious efficiencies and benefits in genetically based rare diseases. Indeed, the approval of small interfering RNA for the treatment of amyloid transthyretin polyneuropathy foreshadows similar success in the treatment of amyloid transthyretin cardiomyopathy, a uniformly fatal disease. Moreover, clinical trial designs for hypertension also presents a potential opportunity for leveraging the advantages of precision medicine strategies. Epigenomic studies in hypertension from the Framingham Heart Study population have demonstrated a precision medicine strategy for defining subphenotypes with hypertension who may benefit from therapies directed against epigenetically modified genes (see section on epigenetics).

Precision medicine leads to precision trials that are smaller but "smarter" versus larger but "dumber."

The recent results of the TAILOR-PCI trial, presented at the 2020 American College of Cardiology's Annual Scientific Session, exemplifies how precision medicine strategies can wield a double-edged sword, simultaneously providing potential breakthroughs and instilling skepticism. This highlights the need for its careful and judicious application in trial design. Clopidogrel, a guideline-recommended P2Y12 receptor inhibitor for dual antiplatelet therapy in the setting of percutaneous coronary interventions (PCI), is a prodrug that requires activation by the hepatic CYP2C19 enzyme. Up to 45% of the general population carry genetic variants of this enzyme leading to poor or intermediate metabolism of clopidogrel, which may lead to stent thrombosis and major adverse cardiovascular events (MACE). Consistent with a precision medicine approach, the aim of the study was to evaluate a prospective genotype-guided strategy and escalation of antiplatelet therapy as needed, compared to standard therapy for patients undergoing percutaneous coronary interventions. In the genotype-guided arm, subjects found to carry a loss-of-function allele for CYP2C19 were treated with ticagrelor, which does not require activation, over clopidogrel. While the study failed to meet its primary endpoint of a 50% reduction in MACE at one year, the genotype-guided cohort demonstrated a 34% risk reduction in MACE and a statistically significant absolute reduction of 2.1% at three months. These findings beg the question whether a 34% reduction should be sufficient to change practice and guidelines, despite what is statistically deemed a study loss.



TOOLS AND APPLICATIONS USED IN PRECISION MEDICINE

The precision medicine approach utilizes a number of non-traditional tools and applications to characterize a person's disease phenotype for disease treatment and prevention.

Genetics and Genomics: Advances in high through-put and next-generation sequencing have increased our understanding of the genetic basis of cardiovascular diseases with the discovery of genetic variants associated with cardiovascular conditions, including hypertension, coronary artery disease, aortic aneurysm, aortic stenosis, and cardiomyopathies. Genome-wide association studies (GWAS) support the concept that complex diseases are commonly associated with genetic heterogeneity, however. While a single pathogenic gene causes a few cardiovascular syndromes, i.e., monogenic, the majority of cardiovascular diseases are a result of complex inheritance and molecular interactions, not attributable to a single gene. GWAS can now provide valuable information on the rare and common variants in subpopulations that affect individual drug responses and their association with a disease phenotype. Moreover, cardiovascular risk scores based on genetic variants are now available for diagnosis and risk stratification for certain diseases.

Higher "omics": The inherited genome only determines part of a person's risk profile. Precision medicine aims to include pan- "omic" analysis to generate a personal "omic" profile.

- *Epigenetics* refers to studies into gene function beyond changes in the DNA sequence. Epigenomics is the study of the complete set of epigenetic modifications on the genome of a cell, i.e., the epigenome. Regulation of gene expression by modifications of the epigenome may also play an important role in disease pathogenesis. Epigenetic modifications are heritable changes to the genome that do not involve changes in DNA sequence, e.g., DNA methylation, post-translational modification of histone tails, and regulation of gene expression by non-coding RNAs. Environmental factors, e.g., intrauterine milieu, diet, smoking, socio-economic circumstances, may lead to epigenetic signals that lead to changes in the epigenetic landscape. Such modifications may affect cardiovascular risk factors.
- *Transcriptomics* is the study of all RNAs or transcripts within an organism. Transcriptome analysis aims to interpret the quantification of transcribed genetic material, including coding and non-coding RNA. This approach serves to capture the impact of tissue type, sequence variation, regulation, environment, external forces (e.g., drugs), and the interactions between them. High-throughput technologies, e.g., RNA microarray and sequencing, allow for assessment of transcript expression at the genome-scale. The transcriptome, thus, provides a snapshot of transcriptional activity under the condition where the RNA was collected, which can be compared before and after drug treatment.
- *Proteomics* is the study of the expression of a large number of proteins in a biological organism. The majority of cardiovascular biomarkers are peptides or proteins, which are currently used as a surrogates of diverse cardiovascular disease processes. Proteomic profiles of several cardiovascular diseases have been reported, e.g., coronary artery disease. By using a comprehensive personal analysis of a validated biomarker, clinical trial designs can then be constructed based on whether that abnormal biomarker predicts patient response to treatment. To some extent, such biomarker-guided trials are being conducted using biomarkers for heart failure and cardiomyopathies, like NT-proBNP and cardiac troponin. However, our application of such biomarkers to patient selection and predictive assessment of drug response is limited by our lack of individualized patient data.
- *Metabolomics* refers to the comprehensive analysis of the expression of small molecules and metabolites in an organism and may be the most accurate gauge of the organism's current state. Contemporary metabolomic technologies, e.g., chromatography and mass spectrometry, can precisely analyze hundreds to thousands of metabolites, providing a characterization of metabolic phenotypes associated with disease and with drug effect. Nevertheless, metabolomics is also vulnerable to confounders, such as exercise and diet. Metabolomics currently lacks research and clinical standardized operating procedures, which leads to variation in sample handling and differences among available metabolomic platforms (e.g., chromatography, mass spectrometry).

Big Data: Traditionally, population registry data, which includes a large number of patients with limited risk factors, have been used to produce cardiovascular risk scores. Moving forward in the precision medicine era, the use of exponentially greater and more granular sources of data, i.e., "big data," will be required for accurate prevention and treatment by the integration of expanding sources of data, including the integration of data from electronic health records, pan- omic data, network analytics, and disease modeling.

Bioinformatics and Modeling: While regression analyses have been often used to test the incremental benefits of new biomarkers, this approach will likely be inadequate to test a large number of biomarkers. Instead, new powerful analytical techniques will be value-added for the rapid and efficient analysis of thousands of biomarkers. Artificial intelligence and machine-learning approaches have been proposed to support such a task. Moreover, modeling techniques can be used to analyze functional and imaging data.

CHALLENGES AND BARRIERS TO PRECISION MEDICINE

Since the introduction of the PMI by President Obama, we have witnessed a boom in technologic advances in the arena of pan- "omics," notably, with revolutionary advances in gene editing (e.g., TALEN, CRISPR-cas), gene silencing (RNA interference), and RNA silencing. While impressive strides have been achieved in clinical trials for hematology and oncology using a patient-specific approach, the story is still developing for the complex pathology of cardiovascular disease, albeit, at a much slower tempo.

A number of barriers to the successful implementation of precision medicine exist. First, given the enormous amount of data from multiple resources and its variability, special considerations must be made for data integrity, accuracy, security, and privacy, as well as data access and timely transfers. For precision medicine to work efficiently and effectively, a comprehensive data integration system will need to be designed, maintained, and validated. While the AHA Precision Medicine Platform represents a nascent start to the integration of large data bases for public access, much of the remaining data sources are unstructured and may be subject to bias or errors, such as medical coding databases and electronic health records.

Secondly, the widespread adoption of a precision medicine approach to cardiovascular medicine naturally requires a demonstration of effectiveness in therapy. The practice of medicine is guided by successful results in clinical trials that result in actionable steps. Most of cardiovascular care is "guideline-based" by medical professional societies through a rigorous evaluation process of published clinical trials. **Thus, the onus remains on all of the stakeholders — physicians, clinical researchers, and clinical trialists — to thoughtfully design clinical trials that demonstrate improved effectiveness in the reduction of cardiovascular disease using a phenotype-based and patient-tailored approach versus standard population-based therapies.** It should be noted that target-based and population-based strategies can and should co-exist. Certain disease processes mandate a population-based approach, while others may only demonstrate significant improvement using a subphenotype-driven strategy.

Thirdly, the issue of healthcare costs presents a complicated barrier — without any easy solution. Increasing the number of person-specific tests and advanced assessments, such as "omic" analysis, poses risks for a considerable increase in health care costs, to the payor, patient, and the health care facilities. Continued funding from governments will be instrumental in pushing precision medicine forward. Reimbursement from third-party payors will require judicious consideration and development and the cost of patient-tailored medicine will require vigorous cost-benefit analysis to address the issue of high-deductibles, copayments, and payor coverage.

Finally, professional and public acceptance plays an important role in the implementation and success of precision medicine in cardiovascular care. Indeed, precision medicine remains a controversial field. Some supporters have openly embraced this new paradigm in cardiovascular medicine, while skeptics and nihilists point to its underperformance and limited niche successes. Ultimately, widespread buy-in will depend on educational programs and a clear demonstration of successful and effective precision medicine treatment strategies. The groundbreaking success in hematology and oncology precision medicine is exemplary of an implementation pathway for other disciplines to follow.

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MEDPACE'S CARDIOVASCULAR PRECISION MEDICINE PROGRAM

Medpace's Cardiovascular Division recognizes the importance of the emerging role of precision medicine in the field of cardiovascular disease. Indeed, we have observed this important and growing trend in cardiovascular clinical trials for the past decade, whereby investigational drugs and therapies are focused on a subphenotype of patients with disease and/or a molecular target, e.g., gene, transcript, or peptide, that is associated with a disease. To optimize support in the design and execution of cardiovascular clinical trials that employ a precision medicine strategy, we have initiated a Cardiovascular Precision Medicine Program (CVPMP). As an extension of the Cardiovascular Division, the CVPMP is comprised of cardiovascular experts with extensive knowledge in the field of precision medicine, who aim to create a highly specialized partnership with industry sponsors seeking to develop therapies focused on disease subphenotypes and employ a patient-tailored approach.

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