

## Review Article



# Challenges and Future in Precision Cardiovascular Medicine

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### Conflict of Interest

The author has no financial conflicts of interest.

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## ABSTRACT

Cardiovascular disease (CVD) still remains the global leading cause of mortality and also impose major burdens on morbidity, quality of life, and societal costs despite of the remarkable progress of cardiovascular (CV) treatment over the past 50 years. CVD therapy improves CV outcomes in less than half of patients. Precision medicine is an attractive and advancing strategy to enhance for disease prevention, diagnosis, and tailored treatment and allocate limited resources more wisely and effectively. We are now in the middle of fourth industrial revolution by a robust confluence of biotechnology, physical science and information technologies. This approach is in its premature so far, but has begun to yield useful information that moves from the conventional 'average response' approach to more specific and targeted approaches governed by individual variability. This review aims to how precision medicine, genomics, and epigenetics work together to create a new era of CV precision medicine.

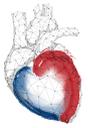
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## WHAT IS PRECISION MEDICINE

The definitions of precision medicine are varying depending on the idea of peoples. A common sense defines precision medicine as new health-care model that facilitates efficient and accurate identification of the optimal health care for individuals. According to the Precision Medicine Initiative, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."<sup>1)</sup>

## PRECISION MEDICINE VERSUS PERSONALIZED MEDICINE

Precision medicine identifies the unique aspects of an individual related to health and disease to choice optimal and effective therapy. We may consider that precision medicine can identify probabilistic risks and the likelihood of various interventions to yield improved health outcomes in patients with common phenotype characteristics. Personalized medicine may refer to implementation of these individual health information into a person-specific



tailored treatment plan or, the creation of a treatment plan for an individual based on known biomarkers.<sup>2-6)</sup> They are not identical, but rather related and overlapping disciplines.

## WHY PRECISION CARDIOVASCULAR (CV) MEDICINE

The current approach to reducing CV morbidity and mortality in at-risk individuals or those with current established CV disease (CVD) is based on a traditional preventive and therapeutic strategies with evidence-based medicine. However, CVD remains the leading cause of mortality and morbidity in the developed countries.<sup>7-9)</sup> According to advances in biological and information sciences in decades, we might expect that more smart and effective strategies for prevention, diagnosis, and treatment could be delivered at both the individual and population levels.<sup>2)3)</sup> However, there is a growing gap of unmet need between the development of biotechnology and clinical application in the global CV healthcare system.<sup>10)</sup> It suggests that significant fundamental changes to existing systems for R&D, translation, and health care delivery are required.

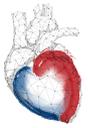
The goal of precision medicine is to identify optimal health care of an individual based on a distinctive personal profile rather than that of the average population. The power of precision medicine depends on the data and requires the synthesis of rapidly changing data sets, ranging from traditional clinical, imaging, and laboratory testing to next-generating sequencing, panomics (genomics, transcriptomics, epigenomics, metabolomics, proteomics, and microbiomics) studies to historical health record data.<sup>11)</sup> For example, using a precision medicine approach, individual undergo deep phenotyping with data analysis performed using network analysis from endophenotype categories to cluster categories. This methodology can be used to optimal changes towards health, predict and prognosticate disease, identify biomarkers for disease, enrich clinical studies, select rational polypharmacy, and optimally tailored environmental exposures.

## PRECISION MEDICINE IN CLINICAL STUDIES

Current clinical trials approach CVDs (e.g. hypertension) by simplifying the biological continuum (e.g. ideal health - CV risk factors - CVD), thereby considering that all trial participants have a common phenotype (e.g. elevated blood pressure), and reporting the trial results as the average finding in a given treatment arm, such as the median blood pressure.<sup>2)12)</sup>

A principle of precision medicine is establishing the precise phenotype for any given health or disease disorder to improve individual and population outcome. Precision medicine focuses on deep profiling of an individual, understanding the determinants of responses to treatments, and finally identifying the optimal treatment tools on the basis of an individual's profile.

Enrichment strategies for more efficient clinical trials are to decrease heterogeneity, or to increase prognostic enrichment, or to increase predictive enrichment. The predictive enrichment strategy utilizes both the characteristics of the trial participant and data obtained either from pre-trial experiments or during the trial (adaptive design) to predict which participants are likely to have a more powerful response to the treatment being tested. This strategy suites the principles of precision medicine and, compared with other enrichment strategies, is likely to result in more efficient clinical trials, improves the benefit–risk



relationship of trial participants, and has the potential to be more informative for daily clinical practice than the other enrichment strategies.

A US Food and Drug Administration guidance document describes 5 categories of predictive enrichment strategies, all of which are applicable to the development of CV therapeutics.<sup>13)</sup>

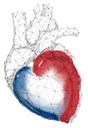
- (1) Empirical strategy: probable responders are selected on the basis of observations during a screening period or on previous responses to the test drug or to drugs from the same class (e.g. Paradigm-heart failure [HF] trial).<sup>14)</sup>
- (2) Pathophysiological strategy: it selects probable responders on the basis of their individual physiology (e.g. Rutherford-2 trial).<sup>15)</sup> Probable responders can also be selected on the basis of the characteristics of the disease under study (e.g. low renin hypertension trial).<sup>16)</sup>
- (3) Empirical genomic strategy: it selects probable responders on the basis of their genetic profile (e.g. Elevate-TIMI 56 trial).<sup>17)</sup>
- (4) Randomized withdrawal strategy: in a randomized withdrawal trial, participants receiving a test treatment for a specified time are randomly assigned to continue that treatment or to discontinue the treatment (switching to placebo can be used to maintain blinding) (e.g. Radiance trial).<sup>18)</sup>
- (5) Studies in non-responders or patients intolerant of other therapy (e.g. Odyssey Alternative trial).<sup>19)</sup>

The use of predictive enrichment strategies for CV clinical trials is expected to increase with advances in systems biology, and network medicine. An important aspect of a predictive enrichment strategy in CV therapeutic trials is the identification of a biomarker.<sup>3)</sup> Biomarkers that predict a clinical end point might ultimately constitute a validated surrogate end point for a clinical trial. As the precision medicine system matures with increasingly complicated biomedical informatics, we could be able to make greater use of the electronic health care record as a bio-research platform. Large, web-based, cohort studies that have the potential to include randomization have also been launched by CV trialists.

## GENOMICS IN CV PRECISION MEDICINE

The CV medical community moves toward more precise and accurate with current diagnoses and treatment, as clinical genome sequencing becomes more common and basic science techniques like clustered regularly interspaced short palindromic repeats (CRISPR) begin to transition toward clinical applicability. Using knowledge gained from population sequencing projects, such as genome-wide association studies, and disease models in the laboratory, we can begin to develop deeper understandings of disease at a molecular level to predict the risk of a patient for developing a CVD and present them with the right preventive and treatment strategy at right time.<sup>20)21)</sup>

CV precision medicine integrates basic science techniques with genomic information as follows: 1) utilization of clinical genome sequencing: genomic sequencing identifies disease-causing mutations in patients and family members (e.g. cascade screening in familial hypercholesterolemia), and direct disease treatment (e.g. long-QT syndrome subtype-informed drug selection) and clarify disease diagnoses<sup>22-24)</sup>; 2) development and evaluation of genetic risk scores: genetic risk scores can help to predict the CV risk of complex disease calculated from the influence of many variants (e.g. in coronary artery disease, CV risk score



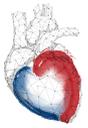
discussion can affect statin usage). Association of genetic risk with CVD outcomes can be as strong as lifestyle risk<sup>25-27</sup>; 3) development of targeted therapeutics: Targeted therapeutics can tackle molecular underpinnings of specific disease subtypes (e.g. PCSK9 inhibition with human monoclonal antibodies in familial hypercholesterolemia. And sequencing can aid placement of patients into appropriate clinical trials<sup>28)29</sup>); 4) CRISPR genome editing and its medical application: CRISPR genome editing can help potential to stop CVD before it starts (e.g. editing in hypertrophic cardiomyopathy [HCM] embryos), and target CVD at the DNA level (e.g. editing of Duchenne muscular dystrophy (DMD) in mice can alleviate disease symptoms)<sup>30)31</sup>); 5) Utilization of CV pharmacogenomics: CV pharmacogenomics can help to individualize CV drug selection and drug use to avoid adverse drug reaction, and to maximize CV drug efficacy<sup>32)33</sup>); and 6) induced pluripotent stem cells (iPSCs) and its medical application; iPSCs can help to make a CVD model and test new therapies in vitro (e.g. testing calmodulin knock-out in long QT syndrome [LQTS]), and potential source of autologous stem cells for transplantation (e.g. iPSC-erythroblasts to treat  $\beta$ -thalassemia).<sup>34</sup> The diagnostic power of genetic testing is significant across the spectrum of CVDs, ranging from cardiomyopathies to life-threatening arrhythmias to aortic disease.<sup>35-37</sup>

In the clinic, genetic testing can 1) clarify CVD diagnoses: genetic testing can help to clarify the diagnosis of diseases that cause similar clinical presentation (e.g., cardiac hypertrophy could be transthyretin (TTR) amyloidosis, Fabry disease, or sarcomeric HCM); 2) facilitate cascade screening: genetic testing can help to identify relatives at risk for CVD before disease symptoms manifest if a disease-associated variant is found on a proband and then screened for in relatives; 3) direct more precise therapy: genetic testing can help physicians choose appropriate treatments and plan the appropriate timing of those treatments. For example, inherited connective tissue disease due to variants in ACTA2, MYH11, or TGFBR2 might prompt consideration of surgical intervention at a smaller aortic aneurysm diameter<sup>38</sup>); and 4) identify patients for targeted therapies: targeted medical therapies, including antibody-based therapeutics, gene editing, and silencing technologies, are available or under development for several genetic diseases, including LQTS, DMD, TTR cardiac amyloidosis, and Fabry disease.<sup>38-40</sup>

## EPIGENETICS IN CV PRECISION MEDICINE

Advances in genetics have identified novel pathways and targets that operate in numerous CVDs, paving the way for precision medicine. However, the inherited genome determines only part of an individual's CV risk profile. Consequently, standard genomic approaches do not take into account the regulation of gene expression by modifications of the epigenome.

Variants in the genes that encode the beta-1 adrenergic receptor (ADRB1) associate with response to beta-blockers in patients with HF. Because the 389Arg allele associates with greater production of cyclic adenosine monophosphate compared with the 389Gly allele, 'hyper-responders' carrying the 389Arg allele might benefit to a greater extent from beta-blockers. An important BEST substudy which investigated the effect of the beta-blocker bucindolol in patients with HF showed that bucindolol reduced mortality and hospitalization in homozygotes for the Arg389 allele compared with the Gly allele carriers.<sup>41</sup> However, MERIT-HF substudy have reported more equivocal results.<sup>42</sup> One Korean HF study showed that the ADRB1 Gly389X genotype showed greater response to bisoprolol than the Arg389Arg genotype, suggesting the potential of individually tailoring  $\beta$ -blocker therapy according to



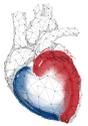
genotype.<sup>43)</sup> Given the heterogeneity in pharmacological properties of beta-blockers in HF, these inconsistencies could reflect differences between these agents or the analysis of a smaller sample size.

The term 'epigenetics' originally embraced the process by which a fertilized zygote develops into a mature, complex organism, but underwent expansion as findings showed that cells having the same DNA can exhibit differential modulation of gene activity. And the transmission of epigenetic changes to daughter cells where it actively regulates gene expression.<sup>44)</sup> Epigenetic modifications defined as 'heritable changes to the genome that do not involve changes in DNA sequence' have emerged as a new aspect of biological regulation in CVD and could advance individualized risk assessment as well as devising and deploying tailored therapies. Genetic mutations acquired during the life course represent an irreversible process, whereas plastic epigenetic changes of DNA/histone complexes are reversible to pharmacological reprogramming. Epigenetic modifications fall into 3 main categories: 1) chemical modifications of DNA (i.e. DNA methylation); 2) post-translational modifications of histone tails; and 3) regulation of gene expression by noncoding RNAs (i.e. microRNAs, PIWI-interacting RNAs, endogenous short interfering RNAs, long non-coding RNAs).<sup>45)46)</sup>

An array of environmental factors significantly contributes to build our individual epigenetic background over time that includes DNA methylation changes, post-translational histone modifications and altered expression of non-coding RNAs. Investigating the individual epigenetic landscape provides an important snapshot of the epigenetic machinery that can be finally used to customize diagnostic and therapeutic approaches in CVD prevention. Available technologies for the study of the epigenome may furnish detailed epigenetic maps based on DNA-histone interactions and non-coding RNAs landscape. Individual epigenetic maps could represent a novel tool in the clinical practice to stratify CV risk beyond traditional or genome-based risk calculations. Epigenetic information also helps in interpreting inter- and intra-personal variation in individual drug response. Adverse epigenetic patterns are modifiable to pharmacological reprogramming of chromatin modifying drugs or non-coding RNAs.<sup>47)</sup>

## CHALLENGES AND FUTURES IN PRECISION MEDICINE

Precision medicine changes the current standard clinical practice and draws from clinical testing, electronic health records, panomics profiling, big data sets, and novel analytical methods, such as systems biology and network science, to create a person-specific phenotype that can be used to identify an optimal treatment.<sup>8)</sup> The obvious benefits of this strategy to patients, clinicians, and researchers are numerous and include individual phenotype specificity, identification of individuals with a similar molecular phenotype, selection of optimal therapies with maximal efficacy and limited adverse reactions, efficient selection and enrichment of clinical trial participants, potential to improve adherence and reduce health care costs, and creating a paradigm shift in how CV care is delivered. To accomplish this goal, the medical community at large, public, big pharmaceutical companies, and other policy-maker stakeholders will need to overcome barriers to implementation that range from technical to social to political.<sup>48)</sup> Other barriers are related to big data set collection and focuses on methods to ensure data accuracy, computational power, security and privacy of data sets, renewal of accruing data, and continuous development and refinement of analytical methods. Finally, continuous education, affordability, and public acceptance of the strategy



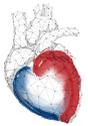
play key roles in its ultimate implementation.<sup>49)50)</sup> Precision medicine is ready to become the next revolution in the medicine, as well as the prevention, diagnosis and treatment of CVD.

## CONCLUSION

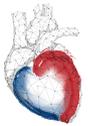
Precision medicine represents a new health care strategy in an integrative approach to disease prevention and treatment. Precision CV medicine comprises basic science and techniques with genomic information; clinical genome sequencing, genetic risk score, genomic editing, targeted therapeutic, and pharmacogenomic. Predictive enrichment strategies for clinical trials utilize both the characteristics of the trial participants and data to predict who is likely to have a more response to the treatments being tested. Epigenetic modifications have emerged as a new landscape of biological regulation in CVD and could advance individualized risk assessment as well as design personalized epigenetic based therapies. Many challenges still remain to be solved in precision CV medicine.

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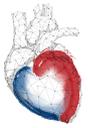
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