Abstract—The Precision Medicine Initiative recently announced by President Barack Obama seeks to move the field of precision medicine more rapidly into clinical care. Precision medicine revolves around the concept of integrating individual-level data including genomics, biomarkers, lifestyle and other environmental factors, wearable device physiological data, and information from electronic health records to ultimately provide better clinical care to individual patients. The Precision Medicine Initiative as currently structured will primarily fund efforts in cancer genomics with longer-term goals of advancing precision medicine to all areas of health, and will be supported through creation of a 1 million person cohort study across the United States. This focused effort on precision medicine provides scientists, clinicians, and patients within the cardiovascular community an opportunity to work together boldly to advance clinical care; the community needs to be aware and engaged in the process as it progresses. This article provides a framework for potential involvement of the cardiovascular community in the Precision Medicine Initiative, while highlighting significant challenges for its successful implementation. (Circulation. 2016;133:226-231. DOI: 10.1161/CIRCULATIONAHA.115.019475.)

Key Words: cardiovascular diseases ■ genetics ■ medicine, precision ■ risk factors

The Precision Medicine Initiative (PMI) was announced by President Barack Obama in his 2015 State of the Union Address. This initiative (if funded) provides an unprecedented opportunity for cardiovascular disease researchers and clinicians to galvanize our collective resources and wisdom, and unite to establish and disseminate the knowledge required to translate discoveries to reduce the global burden of cardiovascular disease in parallel with efforts in other diseases. Concomitantly, it is imperative for the cardiovascular community to be engaged and involved in the PMI and, consequently, the future of precision medicine, while recognizing and addressing the major challenges for implementation into routine clinical practice.

Precision medicine is defined as an evidence-based approach that uses innovative tools and biological and data science to customize disease prevention, detection, and treatment, and improve the effectiveness and quality of patient care. The United States joins other countries including Canada (http://www.genomecanada.ca/en/portfolio/research/2012-competition.aspx), England (http://www.genomicsengland.co.uk), and Estonia (http://www.geenivaramu.ee/en) in making precision medicine a priority. Although research and clinical care that takes genomic and other individual-level differences in account is not new, this broad research program creates an opportunity to leverage technological and scientific advances to develop and rigorously test new approaches for clinical practice.

The coalescence of these goals into the PMI represents a paradigm shift in the vision of the US government and scientific community for the future of healthcare delivery. Achievement of the broader reaching goals of the PMI will likely have significant implications across all medical disciplines. Notably, the cardiovascular community has led discoveries that are aligned with the goals of precision medicine, providing us with a toolbox at our disposal for a personalized approach to promoting health. We are poised to capitalize on the resources and intellectual energy now focused on precision medicine to be partners in this initiative across the diverse issues for science and clinical practice in a disease with enormous national and international public health impact. The new
initiative is an opportunity to expand our current knowledge repertoire and build a substantially larger toolbox that leverages biological and clinical data toward better understanding of disease and better delivery of health care.

This article provides an overview of opportunities for the cardiovascular community in engaging the concept of precision medicine in research and clinical care, detailing a potential framework for short- and long-term goals the cardiovascular community could strive to attain that are aligned with the goals of the PMI across diverse diseases, while highlighting key challenges vital to address to ensure effective implementation of precision medicine. This framework will ideally build on lessons learned from efforts in other countries to minimize the duplication of efforts and create complementary infrastructures for scientific inquiry.

Overview and Near- and Longer-Term Goals of the PMI

Advances in precision medicine have already led to improvements in therapies in certain cancers and in cystic fibrosis, cited as a key example by President Obama, where targeted therapies based on genetic mutations now can treat the underlying cause of the disease. Genomic studies also hold promise for the identification of novel therapeutic targets that could fuel the development of new pharmacological agents for prevention and treatment of disease. For example, after gain of function mutations in PCSK9 were identified as a cause of familial hypercholesterolemia, population studies identified loss-of-function variants associated with lower low-density lipoprotein cholesterol and less coronary artery disease. These studies spurred the development of PCSK9 inhibitors as pharmacological agents that show early promise in atherosclerosis prevention. In addition to genomics, precision medicine extends beyond the use of individual-level genetic data and more broadly includes the study and implementation of using a diversity of other individual-level data in clinical care delivery, such as laboratory data, lifestyle and environmental data, and physiological data from wearable devices. Although the concept, in general, is endorsed by healthcare providers and patients, the practice of precision medicine is currently not in routine use for disease management. President Obama’s initiative will hopefully accelerate the pace of these efforts, test these concepts and produce the necessary scientific evidence, and support implementation for precision medicine to become a commonality in clinical practice across health and different diseases.

The PMI is still in the early planning stages. If the initiative is funded, both near- and long-term goals are outlined. The primary near-term goal is to expand efforts in cancer genomics to prevent and treat more malignancies. The hope is that these approaches will lead to clinical trials using drugs that appropriately target tumor genetics and to understanding and overcoming drug resistance (http://www.cancer.gov/news-events/nci-update/2015/precision-medicine-initiative-2016). The longer-term goals broadly relate to advancing precision medicine to all areas of health with $130 million in non-National Cancer Institute funds planned for these efforts. To support the overall goals, a national cohort study of ≥1 million Americans will be initiated with the goal of setting “the foundation for a new way of doing research that fosters open, responsible data sharing with the highest regard to patient privacy, and that puts engaged participants at the center” (http://www.nih.gov/precisionmedicine). The cohort study will collect biological specimens, clinical data from electronic health records (EHRs), and lifestyle data tracked through mobile health devices. In contrast to other cohort studies, participants will control how the information is used in research and how it is shared, and they will have access to their own data to help inform their own health decisions. This is aligned with the central concept that the patient is at the center of the PMI; patient-reported data and data captured from patients (ie, social media) will all be part of the big data opportunities for tailoring care to the individual. The National Institutes of Health (NIH) held a workshop on “Building a Precision Medicine Research Cohort” (February 11–12, 2015) with world leaders in this field; the report of the PMI Working Group (http://www.nih.gov/precisionmedicine/09172015-pmi-working-group-report.pdf), and public workshops on EHRs, community engagement, and mHealth, as well, are (or will be) available for viewing (http://www.nih.gov/precisionmedicine).

Current State of Precision Cardiovascular Care

So what does this mean for the cardiovascular community? What have we accomplished and how far reaching should our next set of goals be? Cardiovascular disease (CVD) is complex with regard to phenotypic and etiologic heterogeneity. However, if we define precision medicine as medicine that is individualized to the unique clinical and biological makeup of a person, precision medicine is not new to CVD. The cardiovascular community was at the forefront of defining even the concept of a risk factor as early as the 1940s with creation of the Framingham Heart Study (FHS), one of the first of its kind of longitudinal, population-based studies seeking to understand the causes of CVD. The FHS infrastructure, subsequently enhanced by other publically and privately funded large-cohort studies including the Atherosclerosis Risk in Communities (ARIC), the Dallas Heart Study, the Jackson Heart Study, and the Multi-Ethnic Study of Atherosclerosis (MESA), helped develop not only clinical risk scores, but also facilitated seminal discoveries of diagnostic and prognostic circulating biomarkers including cholesterol, brain natriuretic peptide, and troponin. Perhaps the most important genetic risk factor, ie, family history, was also a major discovery from the FHS. More recent studies capitalizing on the infrastructure of these population-based cohorts have identified novel genomic, metabolomics, and proteomic biomarkers that may further facilitate a more personalized approach to cardiovascular care. The NIH-funded Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium has combined clinical phenotypes with existing genetic data from several of these cohorts to facilitate meta-analyses for discovery and validation science, and serves as a model for how integration of large data sets provides more power for common complex genetic diseases.

More recently, a unique population-based infrastructure for cardiovascular discovery has been developed through collaborations between the American Heart Association, academic
medical centers, patient advocacy groups, and private partnerships. The Health eHeart Alliance is an organizational home for patients in the United States interested in heart disease prevention and management. Partnered with the Health eHeart Study, the alliance is enrolling patients across all 50 states in a cardiovascular research study collecting self-reported data, data from wearable personal sensors and online social networks, and other importable big data including genomic and other specimen-derived biological measurements, combined with data from EHRs, and hopes to provide and test an inexpensive platform for testing interventions. These collaborations highlight the need for engagement of diverse communities outside the traditional biomedical partners for precision medicine to truly move forward. Of note, the cardiovascular community has also contributed to the application of pharmacogenetics to individualized care; in recent years, the Food and Drug Administration has added pharmacogenetic labeling to 6 drugs commonly used in the care of patients with heart disease.

Despite the research built from these important studies demonstrating the presence of measurable markers and etiologic heterogeneity in CVD pathogenesis, the one-size-fits-all approach is still broadly used in prevention and management across a variety of forms of congenital and acquired CVD including atherosclerosis, arrhythmia, heart failure, and valvular disease. The cardiovascular community needs to continue to expand its vision of precision medicine and stay abreast of advances in technological, bioinformatics, network medicine, and knowledge systems as applied to research and clinical care. The promise of real-time precision cardiovascular clinical care could become a reality if we embrace these precision medicine tools optimistically, but in a strategic, realistic, and responsible manner, and in close collaboration with scientific communities focused on other diseases.

Precision Cardiovascular Care: The Toolbox

Discovery science and clinical implementation of precision medicine goals involve a complex interplay between individual patients and their health- and disease-related data, health information systems, healthcare providers, and the healthcare delivery system. At its core is a foundation of innovative technologies that facilitate identification, measurement, analysis, and use of individual-level data. This toolbox can be categorized into several strategically focused areas.

The genomics component of the toolbox includes genetic data analyzed by studies such as the CHARGE consortium and catalogued in large publically available databases including the database of Genotypes and Phenotypes (dbGAP) and 1000 genomes. The Clinical Genome Resource (ClinGen) project represents an NIH-funded project curating research and clinical genetic testing data associated with specific diseases. ClinVar is a partner of the ClinGen project that facilitates access to the data. Databases such as ClinGen and ClinVar provide infrastructure and standards to support curation of genetic variants and archive reports of genotype-phenotype correlations to facilitate clinical use of this genetic data. Although less advanced, similar efforts are beginning in other omic biomarker technologies such as metabolomics, epigenetics, transcriptomics, and proteomics.

Although often viewed as the same as genomic medicine, precision medicine extends far beyond genomic medicine to encompass a wide variety of individual-level clinical and lifestyle data. The broad implementation of EHRs provides us with another tool and an unparalleled opportunity to study population- and individual-level risk factors, exposures, family history, lifestyle, and response to medications, with biological and physiological data. The next wave of EHR-based research and clinical care will need to integrate genetic data including large-scale genome-wide data to use throughout a patient’s lifetime to guide risk stratification, selection of medications with the optimal efficacy and minimal side-effect profile for that individual, and personalization of lifestyle choices for maximal health benefit. EHRs will also likely include deep physiological data from wearable or implantable technological devices including heart rate variability, accelerometry, and blood pressure. Integrated EHRs thus have the potential to be a novel source of data for clinical and translational researchers for data and pattern mining from which to build better multi-marker disease risk prediction models, to identify patients for clinical trials, to identify novel phenotypes of health, disease, and drug response by using molecular and clinical data, and to create the infrastructure to enable systematic identification of patients in need of targeted clinical diagnostics or treatments. Efforts in this realm are already underway including the Electronic Medical Records and Genomics (eMERGE) Network, a National Human Genome Research Institute–funded consortium.

Digital technologies are becoming increasingly used for healthcare studies and clinical care and thus are also an important precision medicine tool. These emerging electronic communication and information technologies, broadly termed eHealth, include the Internet and mHealth (mobile phones and wearable devices for interactive communication and monitoring of physiological and other data). The longitudinal, high-dimensional data extracted from such technologies, combined with the potential for 2-way real-time interactions between patients and healthcare providers, hold promise for more granular and dynamic individualized care. Although small studies have inconsistently suggested these devices can improve outcomes in cardiovascular and other diseases, larger-scale studies of the accuracy and efficacy of these devices will be vital before their use in a broader precision medicine approach. Ideally, these studies would be conducted under the auspices of the PMI.

The integration and use of the multidimensional data extracted from EHR and mHealth technologies, coupled with large-scale biological data, necessitates a dedicated effort around the development of analytic and bioinformatics methods as part of the precision medicine toolbox, to support the clinician and researcher in the application of relevant knowledge to the bedside. The rapid growth in medical information systems, and industry investment, as well, in developing artificial intelligence tools has been spurred by the recognition of such healthcare demands in the area of data-driven medicine. Investment in novel technologies will also likely enable new discoveries as tools that are potentially translatable to clinical care, such as the creation of cardiac and induced pluripotent stem cell biorepositories from patients with...
different cardiac diseases and the development of sequencing
and biomarker point-of-care tests. Genome-editing strategies
are being used to develop very precise models of disease in
model organisms, and in patient cells, as well. Another exam-
ple includes technologies such as 3-dimensional printing that
allow creation of 3-dimensional cardiac models for structural
heart defects that can inform the surgeon preoperatively of the
unique anatomic characteristics of the patient and improve the
precision of cardiac surgery.

Opportunities and Challenges for the
Cardiovascular Community in the PMI
Although the opportunities for discovery and implementation
science for cardiovascular and other diseases within the PMI
are many and broad reaching, we believe there are vital inves-
tigations central to achieving the goal of precision medicine
becoming a part of everyday clinical care. Balanced with these
provocative opportunities, the success of the PMI will be predi-
cated on addressing key challenges across diverse components.

Perhaps one of the most obvious and important opportuni-
ties is for the involvement and engagement of the cardiovas-
cular community in the cohort study proposed and funded by the
PMI. This would ideally include participation in study subject
recruitment and input on cardiovascular-related data collection
and phenotype harmonization, balancing consistent and
precise definitions with the ability to account explicitly for
evaluate endophenotypes and disease-related risk factors.
The large cohort study will, no doubt, create a vast number of
research opportunities; early involvement by the cardiovascular
community will therefore be important to rapidly capital-
ize on these opportunities.

One of the most important opportunities, but also a chal-
lenge for precision medicine, involves the application of
genetics to clinical care. Whereas sequencing studies and
more widespread use of clinical genetic testing continues
to identify novel genetic variants, the lack of information
about pathogenicity of the majority of these variants is a
critical barrier to the translation of these findings to clinical
care. A more systematic, dedicated approach to determining
genetic causality involving genotype-phenotype correlation
(including disease phenotypes and drug response and adverse
effects), bioinformatic approaches, and functional evaluation
in vivo and in vitro models needs to be pursued, ideally
through collaborative partnerships between academia, the
government, and industry (eg, genetic testing companies). In
addition, efforts around genomic and other biological data
discovery science should occur in parallel with support for
well-designed studies to test the efficacy and effectiveness
of precision medicine approaches in improving clinical care,
whether in improving symptoms, quality of life, health out-
comes, or cost of healthcare delivery. Concomitantly, imple-
mentation science evaluating existing and novel methods for
the integration of precision medicine technologies into every
day clinical care should be performed so that health delivery
systems will be ready to implement precision medicine tech-
nologies showing evidence-based value. Francis Collins and
Harold Varmus importantly note that a key foundation to pre-
cision medicine becoming a reality across disease phenotypes
necessitates advancing the nation’s regulatory frameworks.
The NIH, in conjunction with the Department of Health and
Human Services, is working to bring the Common Rule,
originally designed to protect research participants, more in
line with contemporary participants’ desire to be active part-
ners in modern science. Partially spurred by the PMI, the
Food and Drug Administration has been entertaining creative
approaches to the balance between genomic innovation and
patient safety that could include nontraditional ways of evalu-
ating genomic tests for analytic validity (ie, by capitalizing
on the large amount of next-generation sequencing data) and
clinically meaningful tests (ie, by creating and mining large
databases linking genes with clinical data).

Another opportunity in precision medicine revolves
around the improvement in information technology systems
used in research and clinical care; such systems are integral to
discovery and implementation science and healthcare delivery.
The scale of the PMI effort likely necessitates a complete inte-
gration of the disparate information systems used in research
and clinical care to achieve these goals. In addition, the infor-
mation technology components of precision medicine need to
cautiously balance ideals for ease of data uploading and data
sharing to maximize scientific discovery with appropriate care
taken to protect patient privacy. Relatedly, acquiring, curating,
and understanding patient biological and phenotypic data rep-
resent another important challenge. The PMI will bring pheno-
type data to the same scale as genotype data and facilitate
discrimination of these biologically and clinically meaningful
genotype-phenotype correlations. These challenges highlight
opportunities for early career investigators, genome scientists,
and new areas of computer science and engineering experts to
work together toward solutions for the future.

With this increasing complexity and scale of individual-level
data, however, come challenges of cost for discovery science
and implementation. Despite the anticipated allocation of sig-
nificant financial resources to the PMI, the overarching program
would likely exceed those costs manifold, necessitating strong
but carefully structured public (ie, NIH, academic medical
centers) and private (pharmaceutical and biotechnology com-
panies) partnerships with tangible commitments to continued
resource needs. For example, one opportunity for encouraging
such partnerships is to link genetic data with clinical pheno-
types and to curate effectively these data in a useful way, such
as being done in ClinGen and Clinvar and the American Heart
Association’s Cardiovascular Genome-Phenome project which
integrates the American Heart Association with philanthropic
and industry funding. These integrated efforts have also led to
the creation by the American Heart Association of the Institute
for Precision Cardiovascular Medicine, which seeks to address
many of these important issues in precision medicine.

Finally, an important opportunity for precision medicine
across CVD and all medical disciplines, but with its own
share of challenges, is education of the taskforce. Although
interdisciplinary teams are vital for knowledge discovery in
precision medicine, the practice of patient care stands in the
hands of the healthcare provider and the healthcare consumer.
As a cardiovascular community, a goal may be to educate
trainees in precision medicine. A second equally important
goal may be to ensure that the application protects patients’
wishes and privacy. Initiatives for clinician education in genetics are thus not only a vital foundation, but also a potential bottleneck, for the ultimate goal of providing individualized patient care on a daily basis. Vast new data sets with diverse discoveries built on high dimensional clinical and molecular data but with no clear approach to communication of results in an actionable format to the regular provider, and without provider education for how to use those results clinically, could be antithetical to achieving the goals of precision medicine.

The National Institutes of Health Genomic Research Institute, the Institute of Medicine, and the American Heart Association have devoted time and effort to achieving this mission for education in genomics for healthcare providers.

We propose a diverse agenda of potential short- (1–2 years), medium- (2–5 years), and long-term (10–20 years) goals broadly related to CVD that could be accomplished through the PMI (Table). Of note, a cultural and logistic change to an integrated approach to research and clinical care is central to the goals outlined below. A final question we need to keep in mind is how much improvement will the patient see when cardiovascular healthcare providers apply multidimensional data to the clinical visit? Application of these multiple data points for each individual patient will hopefully help determine the best cholesterol or antiplatelet medication, the best method for weight loss interventions, the most appropriate type of aortic valve replacement and whether it is done percutaneously or surgically, and personalized mechanical device therapies in patients with heart failure. These data may provide richer phenotypes for use in research and clinical care, potentially enabling discoveries not possible with our previous data collection techniques.

**Conclusion**

CVD has broad and profound public health implications across the United States and abroad. We as a cardiovascular community have already contributed seminal discoveries that could have important implications for precision medicine. President Obama’s PMI will accelerate the trajectory for this goal of

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**Table. Proposed Potential Short-, Medium- and Longer-Term Goals for Cardiovascular Disease in the Precision Medicine Initiative**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Goal</th>
<th>Time Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models for health and disease</td>
<td>Development of integrated clinico-omic models of disease progression/outcomes</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td>Development of integrated clinico-omic models for disease risk and diagnostics</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Development of integrated clinico-omic models for determining patient-oriented outcomes (functional status, quality of life)</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Validation of existing and ongoing discoveries in the PMI cohort</td>
<td>Medium</td>
</tr>
<tr>
<td>Information systems and technologies</td>
<td>Information systems for annotation and integration of data from wearable and ambient technologies to create novel computable phenotypes and merge with EHR in a clinically useful format for cardiovascular providers</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td>Validation of accuracy of measured data</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td>Creation of systems of education to facilitate providers’ use of the data</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Studies to prove that use of data improves relevant outcomes</td>
<td>Long</td>
</tr>
<tr>
<td>Genetic and molecular discoveries</td>
<td>Genetic studies of rare or extreme cardiovascular phenotypes</td>
<td>Short</td>
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<tr>
<td></td>
<td>Creation and validation of polygenic models of common and rare CVDs</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Application of next-generation sequencing to the genetic etiology of cardiomyopathies and congenital heart disease for new diagnostics (including prenatal genetics) and molecular targeted therapeutics</td>
<td>Medium</td>
</tr>
<tr>
<td>Environmental underpinnings of CVD</td>
<td>To create systematic and validated approaches for collection of exposome data (measure of all exposures of an individual across a lifetime, including environmental and occupational exposures) relevant to CVD</td>
<td>Medium</td>
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<tr>
<td></td>
<td>Larger and more comprehensive studies of gene-environment interactions</td>
<td>Medium</td>
</tr>
<tr>
<td>Human systems biology and network medicine</td>
<td>Development and experimental validation of bioinformatics approaches to molecular data integration</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Vertical integration of basic science data</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Expansion of the human interactome and its application to defining disease modules and pathways within which genetic variants may be operative</td>
<td>Medium and Long</td>
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<tr>
<td></td>
<td>Mathematical approaches for pattern recognition in combined multidimensional clinical, lifestyle and molecular data</td>
<td>Long</td>
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<tr>
<td></td>
<td>Evidence-based studies of use of biomarkers and risk models for guiding pharmacological and lifestyle treatment</td>
<td>Long</td>
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<tr>
<td>Clinical translation of discoveries</td>
<td>Development of models and infrastructure for cardiovascular genomics clinics</td>
<td>Short</td>
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<tr>
<td></td>
<td>Development of point-of-care technologies for molecular biomarker testing</td>
<td>Long</td>
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<tr>
<td></td>
<td>Novel pharmacological target discovery</td>
<td>Long</td>
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<tr>
<td></td>
<td>Application of the human interactome network to assess drug target function holistically, to ascertain potential off-target effects, and to identify rational polypharmaceutical approaches to the treatment of complex CVD phenotypes</td>
<td>Long</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; EHR, electronic health record; and PMI, Precision Medicine Initiative.
transforming clinical care. We need to approach these endeavors carefully, but with innovation, creativity, and responsibility, to ensure that hype does not overshadow reality. We also must continue to approach these endeavors as thoughtful researchers; even well-known mutations within families demonstrate remarkable heterogeneity in disease expression, and we have known for decades that penetrance of mutations is highly variable. We need to be involved and engaged in the precision medicine process so that this important disease has an explicit and specific place at the table. We have provided a framework for mechanisms in which the cardiovascular community could be involved, and we encourage this involvement so that we, too, can provide the best care for cardiovascular health and disease prevention.

Disclosures

None.

References


Opportunities for the Cardiovascular Community in the Precision Medicine Initiative
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