JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. 1, NO. 4, 2016

ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2016.05.003

EDITOR'S PAGE

Will the Precision Medicine Initiative Transform Cardiovascular Translational Research?

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President Obama announced in his 2015 State of the Union address that he was launching the Precision Medicine Initiative (PMI), calling it "a bold new research effort to revolutionize how we improve health and treat disease" (1). Under the auspices of the PMI, the National Institutes of Health will create a U.S. cohort of 1 million participants who voluntarily contribute information about their medical and social history, environment, and life-style and provide biospecimens for genetic and other future molecular characterization. This information will ultimately be available to the scientific community with the hope that it will be used to develop novel new therapies and identify novel approaches to disease prevention. In parallel, the National, Heart, Lung, and Blood Institute has developed a major research initiative, TransOmics for Precision Medicine (TOPMed), that will "couple whole-genome sequencing (WGS) and other -omics data with molecular, behavioral, imaging, environmental, and clinical data from studies focused on heart, lung, blood and sleep disorders" (2). The long-term goal of TOPMed is to uncover factors that "increase or decrease the risk of disease, identify subtypes of disease, and develop more targeted and personalized treatments" (2). Concurrently, the U.S. Food and Drug Administration (FDA) has created the precisionFDA initiative to facilitate the development and standardization of next-generation precision diagnostics and inform advances in regulatory science to benefit individuals and public health. The goal of precisionFDA is to create a "community research and development portal that allows for testing, piloting, and validating existing and new bioinformatics approaches to next generation sequence processing" (3). With all of the excitement around these big science initiatives and precision health care, it is appropriate to question whether these new programs will accelerate translational research efforts to develop new drugs and devices for patients afflicted with cardiovascular disease.

Unlike cancer, the efforts thus far to use genomic data to inform the development of *personalized* cardiovascular therapeutics have been promissory. The Personalized Medicine Coalition reported that 13 of the 45 novel new drugs approved by the FDA's Center for Drug Evaluation and Research in 2015 could be classified as "personalized medicines" (4). A total of 5 of the 13 new drugs classified as personalized medicines were oncology drugs, accounting for 35% of the new oncology drugs approved by the FDA in 2015. By way of comparison, only 4 novel new cardiovascular drugs were approved by the FDA in 2015, none of which were classified as personalized medicines. Perhaps more sobering is the realization that more than a decade after the completion of the Human Genome Project, we still do not have a single new life-extending cardiovascular treatment emanating from this nearly $3 billion effort. As a result, many skeptics have argued that, analogous to the Human Genome Project, the champions of PMI are overpromising on the deliverables. Given the glacial progress in the cardiovascular space thus far, this argument is certainly understandable.

Notwithstanding the discovery of PCSK9 (5,6) and the elegant translational efforts that followed (7), our ability to use "omic" technologies to develop novel cardiovascular therapeutics has been slow in comparison with the development of novel new cancer drugs. In this regard, the PMI may create several exciting new opportunities for cardiovascular translational investigators. First, the ability to use high-dimensional genomic data should provide a unique opportunity to identify enriched patient populations for future treatment trials, as well as novel drug targets. As 1 potential example, a post-hoc genome-wide association

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study of patients from the dalcetrapib arm of the dal-OUTCOMES trial, which was neutral with respect to the primary endpoint (8), identified a unique group of responders who had a single nucleotide polymorphism in the ADCY9 gene (9). This pharmacogenomics analysis formed the rationale for the forthcoming 5,000-patient phase 3 multicenter trial (Effect of Dalcetrapib vs Placebo on CV Risk in a Genetically Defined Population With a Recent ACS [dal-GenE]; NCT02525939) that will examine the effects of dalcetrapib in subjects recently hospitalized for an acute coronary syndrome who have the appropriate genetic profile. Second, the precisionFDA initiative will promote standardization of next-generation sequencing platforms, which in turn will allow investigators to combine genetic information obtained from multiple datasets. Third, the National, Heart, Lung, and Blood Institute's TOPMed initiative will develop the requisite infrastructure to create data warehouses from existing well-curated patient cohorts (e.g., Framingham Heart Study and the Jackson Heart Study), enabling investigators to combine phenotypic, genomic, and sociocultural data in a heretofore unprecedented manner. The use of these integrated data platforms may allow researchers to better understand how subjects respond to conventional cardiovascular therapies and may offer the possibility to better understand how interactions among comorbidities, life-styles, and sociocultural backgrounds influence the outcomes of individuals with a given genetic profile. Although transgenic animal models have provided invaluable mechanistic insights into diseases and permit rigorous mechanistic experimentation, they are less valuable for translational efforts. Transgenic mice are highly inbred and lack the genetic heterogeneity in humans, and laboratory environments lack the diversity of human environmental exposures. Mice are also devoid of the types of comorbidities that negatively influence the outcomes of patients with cardiovascular diseases. Fourth, the ability to perform whole genome sequencing in different patient populations will allow scientists to better understand the natural consequences of gain- or loss-of-function mutations in genes that are associated with different cardiovascular diseases. Thus, the PMI should provide a unique opportunity to better understand the drivers of human disease and to potentially identify new cardiovascular drug targets.

WILL THE PMI TRANSFORM CARDIOVASCULAR TRANSLATIONAL RESEARCH?

At this point in the life cycle of the PMI, any attempt to answer this question would be completely hypothetical. Further, given that the majority of cardiovascular diseases are influenced by multiple genes and macro-environmental and microenvironmental features, the road ahead for cardiovascular translationalists will likely have considerably more twists, turns, and bumps than the road traversed by our translational colleagues in oncology. However, with that said, the PMI will place a new set of unique tools and techniques in the hands of both cardiovascular investigators in academia and industry, as well as patient advocacy groups. Although these new tools and the opportunities they bring may not be transformative immediately, they will certainly advance the field in a number of exciting and unforeseen ways in the coming years. As always, we welcome your thoughts, and would like to hear what you think about the effect of the PMI on cardiovascular translational medicine, either through social media (*#JACCBTS*) or by e-mail (jaccbts@acc.org).

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