Cardiovascular precision medicine: hope or hype?

Dr Geoffrey S. Pitt discusses the successes of precision medicine to date and its potential for the future.

An ever-growing number of studies and editorials herald the promise of ‘precision medicine’. On the diagnostic side, new technologies and analytical tools will allow us to pinpoint patient-specific differences and on the treatment side novel therapies will permit us to exploit those differences for better outcomes.

A combination of genomic, epigenomic, transcriptomic, and metabolomics information—a patient’s ‘panomic’ data—may soon be part of an individual medical record. And innovative therapies such as ivacaftor, a cystic fibrosis treatment that targets only a small set of mutations in the CFTR gene, could be weapons in our treatment armamentarium to provide the ‘right drug in the right dose at the right time’.

When US President Barack Obama spotlighted such opportunities by launching his new Precision Medicine Initiative in January 2015, he focused upon opportunities in cancer and diabetes. How will precision medicine fit into cardiology?

Advances in precision medicine will likely accrue to cardiology rapidly. While our field was not a focus of the initial excitement surrounding the Precision Medicine Initiative announcement, I believe cardiology is poised to be a leader in the development of this discipline, based upon more than half a century of contributions. Indeed, the pioneering Framingham Study was instrumental in introducing the concept of disease prediction based upon patient-specific data or ‘factors of risk’—serum cholesterol and blood pressure. Large randomized clinical trials, another innovation grounded in cardiology, provided additional data sets mined for markers of risk and for new therapeutic strategies.

Subgroup analysis of the V-HeFT trial in which vasodilator treatment with hydralazine/isosorbide dinitrate combination vs. prazosin or placebo showed a 34% reduction in mortality from heart failure is a prime example. Post hoc analysis revealed an especially strong effect among patients who identified themselves as black. Along with studies showing lower nitric oxide bioavailability and decreased nitric oxide sensitivity in blacks, a randomized controlled trial of hydralazine/isosorbide dinitrate combination therapy in black patients revealed a 43% improvement in survival and led to approval by the US Federal Drug Administration (FDA) of combination therapy for heart failure specifically in black patients.

Similarly, mining of clinical trial data led to development of the CHA2DS2-VASc scoring system, which allows individualized anticoagulation therapy for prevention of thromboembolic stroke in atrial fibrillation. Patient-specific therapy in cardiology also extends to devices, such as individual programming and adjusting of pacemakers, so that we should broaden our definition to the ‘right device or drug, with the right settings or in the right dose, at the right time’.

Cardiology has also been a trailblazer in applying some of the newer tools of precision medicine. The identification of specific genetic loci associated with congenital long-QT syndrome afforded a platform for genotype–phenotype correlations. For example long-QT patients with mutations in the potassium channel gene KCNQ1 most often experience events during exercise and rarely during sleep while the trigger for long-QT patients with mutations in the sodium-channel gene SCN5A is most often sleep and rarely exercise. Beta-blockade has been the mainstay of therapy for patients with congenital long QT syndrome but ‘late’ sodium channel current blockers appear to be uniquely efficacious in patients identified with SCN5A mutations. Such genotype-guided therapy is every bit as precise as the developing strategies for mutation-guided cancer therapy.

So, what is on the horizon for cardiovascular precision medicine? One major goal will be to tackle the cornerstones of heart disease, such as hypertension or coronary artery disease. Despite their strong inheritability, uncovering a genetic signature for hypertension or coronary artery disease that can lead to meaningful interventions has been challenging because of the underlying genetic complexity. It is a problem of numbers: any single genetic variant contributes only a small amount of information. Further, even in the largest of the recent genetic studies only a few genetic variants meet the strict statistical thresholds for significance, thus leaving us with a limited numbers of variants contributing only a small increase to risk stratification algorithms beyond the traditional coronary artery disease risk factors. To overcome these hurdles new statistical methods and analysis paradigms need to be developed and implemented.

One promising approach under investigation is to add orthogonal data, such as information from commonly obtained blood tests, functional data, or some of the new ‘panomic’ data sets (e.g. metabolomics, transcriptomics, or signatures from our microbiomes).
With complex analytical approaches, such as hierarchical cluster analysis, one can uncover new disease signatures, provide novel risk stratification algorithms, or develop diagnostic approaches. This ‘big data’ approach allows the recognition of patterns that are not obvious using our standard clinical and diagnostic approaches. One excellent example is a recent study that analysed heart failure patients with preserved ejection fraction (HfPEF) across 46 different variables. Heart failure patients with preserved ejection fraction is a notoriously heterogeneous disease, but this study was able to identify three distinct groups with widely different outcomes. We should also be poised to capture and utilize the flood of real-time data from wearable fitness trackers and implanted sensors. Such device data add a temporal dynamic to risk stratification and treatment paradigms. Determining whether a patient continues to have paroxysmal atrial fibrillation, and whether to continue anticoagulation therapy, may be as simple as checking a smartphone app.

As a new flood of panomic data enters our treatment algorithms, there are bound to be missteps as well as successes, and indeed cardiology has already seen some examples. Since genetic polymorphism at CYP2C19 affects the levels of the active metabolite clopidogrel, determining a patient’s genotype promised to help guide antiplatelet therapy and led to a US FDA ‘Black Box’ warning with a suggestion to consider genetic testing. Nevertheless, polymorphism-guided antiplatelet therapy has not proved successful. In a similar manner, we are just beginning to develop strategies to respond to incidental genetic findings. Six per cent of asymptomatic and apparently normal individuals harbour a protein-altering missense mutation in KCNQ1, KCHN2, or SCNSA, the three major long QT syndrome loci. Such a high mutation rate invariably leads to diagnostic and therapeutic dilemmas when patients with no syncope and no family history of sudden death are incidentally discovered after whole-exome sequencing for an unrelated condition to have a mutation in one of those genes. Until we develop better means to correlate specific genetic variants with disease risk, we will be challenged to respond appropriately to what promises to be an escalating number of cases. For this, it will be wise to apply Bayesian principles, such as those that have already proven useful to decrease false positives in exercise treadmill testing for coronary artery disease.

Even with these cautions, one can imagine that general approaches such as those advocated for statin therapy in the 2013 American College of Cardiology–American Heart Association (ACC-AHA) Task Force on Practice Guidelines will soon transition to more individualized therapeutic approaches decisions informed by precision medicine tools. In the ongoing battle between lumpers and splitters, it looks like the splitters will win. Precision medicine will hit the bull’s eye.

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References
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Editors’ network of the European Society of Cardiology National Cardiovascular Journals: scientific input from the National Societies

Scientific relevance and current activities are discussed by Fernando Alfonso, MD, FESC, Chairman of the Editors’ Network

National Society Cardiovascular Journals (NSCJs) are the official journals from the corresponding national societies of the European Society of Cardiology (ESC). NSCJs have major scientific value as they publish original high-quality scientific research, but they also play a unique role in education by publishing state-of-the-art review papers, viewpoints, and related materials. However, NSCJs are quite heterogeneous in size and scope and most of them publish in the local languages. In addition, NSCJs remain completely independent as they belong to the corresponding ESC national societies (http://www.escardio.org/membership/national-societies/Pages/journals.aspx#nat-journals).

In this regard, NSCJs provide a unique tool to further disseminate scientific content and educational material with the attractive feature of being able to reach the level of the practicing physician working in the different countries. However, over the years many of these journals have also gained international prestige and scientific recognition and include English editions. Overall, up to 23 NSCJs are currently listed in PubMed and 12 of them have obtained an impact factor on the Thomson Reuters ISI Web of Science database. Therefore, NSCJs clearly complement the ESC official journals by disseminating novel cardiovascular research and by helping to