A view from the side-line

A look into the reasons and the genetics involved, for the future of precision medicine

Just over a year ago, I predicted that cardiology would soon be swept up in the march towards precision medicine. While precision medicine is not yet here, neither in cardiology nor any other medical discipline, numerous advances preserve my optimism and bolster my confidence that we will experience a fundamental shift in how we practice cardiology within the next 5 years.

Before sharing some observations, a caveat: I am not a precision medicine expert. My main professional focus is research on the molecular mechanisms of cardiac arrhythmias due to ion channel mutations, and my clinical practice is partly dedicated to treating patients with inherited arrhythmias. Thus, I have had a longstanding interest in genetics, the field in which initial advances triggered the precision medicine wave. So, here I offer an interested outsider’s perspective on how we will continue to move towards the golden paradigm of ‘delivering the right drug in the right dose to the right patient at the right time’.

It is on the back of rapidly decreasing costs of gene sequencing technologies that precision medicine promises have been made. With next-generation sequencing, we can now easily query variants across many loci (or all variants at all loci, if whole exome or whole-genome sequencing is applied) to uncover genetic differences among patients presenting with otherwise similar phenotypes.

Long QT syndrome, once thought to be a single disorder, is now appreciated as a common clinical manifestation of mutations in more than a dozen distinct genes, many with specific corresponding genotype-phenotype correlations. While most of these advances in Long QT syndrome predated the next-generation sequencing era, this general principle—distinguishing genetic subsets of what was thought to be a single entity—can have profound importance for genotype-specific responses to drug therapy. Cancer therapy, for example, is being revolutionized by tailoring therapeutic interventions based on the presence of specific driver mutations present in a tumour.

In the Long QT syndrome example, implementation of β blocker therapy for mutations in the K⁺ channel genes KCNQ1 or KCNH2 vs. late sodium current inhibitors for mutations in the Na⁺ channel gene SCN5A show the advantages of distinguishing among underlying genetic contributions and thereby defining specific molecular pathways for targeted therapeutic intervention.

The early successes in defining distinct genetic subsets in Long QT syndrome came from classical genetic approaches that exploited large kindreds and the accompanying statistical power to find associated genes. Next-generation sequencing, whole exome or whole genome, can be effectively applied to smaller kindreds. Recent successes include the identification of mutations in the gene for mitochondrial nicotinamide nucleotide transhydrogenase as one cause of left ventricular noncompaction and the report of mutations in several new candidate loci associated with various familial congenital heart defects.

One version of this technique focuses on even smaller units: the trio of an affected child and his/her unaffected parents, a method particularly well-suited to look for de novo mutations. This approach was successfully applied to find a significant fraction of sporadic congenital heart defects arising from mutations in genes controlling histone modification (a process that turns transcription genes on or off).

With trios, variants found in an affected child are filtered by those present in the parents, leaving a more manageable list of candidate genes for further investigation that can be whittled to a likely causal gene by additional filtering algorithms, including functional testing. These filtering algorithms are essential, since recent data from the 1000 Genomes Project predict that each of us differs from the reference human genome at 4 000 000–5 000 000 sites, including almost 200 variants that encode protein truncation and an additional 10 000 variants that change the amino acid sequence of a specific protein.

The challenge becomes immediately obvious when thinking about how to use all of this information for a patient in clinic who presents with her genome and questions about disease risk or prognosis. Which of the many variants are meaningful?

While this clinical scenario has not yet arrived, I predict that it will be soon. I also side with those who believe that the inherent challenges will be surmountable, aided by two advances.

First, investigators are collecting more genomes with well-annotated clinical data. As this pool grows sufficiently, researchers will be able to group patients with a specific clinical presentation or stereotypic response to a therapy and identify which specific variants or sets of variants correlate with the clinical presentation or therapeutic outcome.

Second, I anticipate rapid clinical implementation once the utility of using genomic information becomes clear for even a subset of clinical scenarios. In a virtuous cycle, the new genomes of patients made available as implementation ramps up will be mined for additional correlations to fine tune how we diagnose and treat patients. A recent study in Lancet provides a tantalizing hint. Using a panel of 27 genetic variants, Mega et al. were able to risk-stratify patients for incident and recurrent coronary heart disease events and showed that the highest-risk category derived the most benefit from stent therapy.

With genetic information, more is better: more variants and more genomes. Based on this success with 27 variants, imagine what could be distilled from whole-exome or whole-genome data supported by the statistical power of a sufficient number of genomes. While there will be a diminishing return at some point as more variants are included, a lot of the risk remains unexplained with this 27 variant panel. Using next-generation, sequencing provides an unbiased means to uncover many important, and unexpected, additional variants to risk stratify more accurately.

While additional genomic information will boost predictive power, the march towards precision medicine will ultimately be paved with...
more than genomics, which is but one of the molecular profiling platforms being investigated. Epigenomics (analysis of changes in factors regulating gene transcription that are not encoded by the genome—such as, histone modification), transcriptomics (investigation of changes in the level gene transcription), proteomics (measurement of protein levels or protein modifications, such as site-specific phosphorylation), and metabolomics (quantification of change in small metabolites) are examples of additional dimensions to the data array that will serve to differentiate patients for diagnosis and treatment.

While lagging behind genomics in ease of obtaining data and analysis, these platforms are rapidly gaining ability to add to the predictive power offered by genomics. Importantly, these additional platforms are dynamic. They change with disease state and interventions, unlike the static genome (other than for tumours, wherein genetic change is a hallmark of the disease process). Querying one or more of these other platforms before and after therapy will add significant context to the predictive power of genomic profiling.

A final note for now. Critical to all of the investigations that will weave a web of molecular profiles into power predictive algorithms is the availability of precise and accurate phenotypic data. Deeper sets of clinical variables yield more opportunities to generate meaningful correlations with various molecular profiling data. The absence of deep phenotypic data threatens to slow the progression toward precision medicine. While the ongoing and rapid adoption of electronic medical record (EMR) systems offers an opportunity to capture more phenotypic data and utilize it for precision medicine, EMRs have not yet been fully exploited. As these EMR kinks become straightened, it will be a quicker path towards implementation of precision medicine in cardiology.

References
References are available as supplementary material at European Heart Journal online.

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The Rene Laennec Lecture at ESC Congress 2016

Professor Helmut Baumgartner presented the Rene Laennec Lecture on Clinical Cardiology at ESC 2016 in Rome

In recent years, the population of aortic stenosis (AS) patients that cardiologists are being faced with has changed, and with that the challenges and treatment options.

It is this changing landscape that Prof Helmut Baumgartner will discuss as he presents the ESC Rene Laennec Lecture on Clinical Cardiology at ESC 2016 in Rome.

Entitled ‘Aortic stenosis—A “simple” heart defect with ongoing diagnostic and therapeutic challenges?’ he will address three major issues: how to diagnose severe AS correctly; when to intervene in severe AS; and how to intervene.

He said: ‘During the early days of my career the main question was, do we need invasive evaluation or can this be adequately performed by echo.’

While it took some time to answer this, echo did replace catheterization and become the gold standard with the definition of severe AS by mean gradient <50 and later 40 mmHg and a valve area <1.0 cm² becoming well accepted. It was also recognized that patients with poor LVEF and reduced flow may present with low gradients and require dobutamine echo to distinguish between true severe and pseudo severe AS.

However, Helmut Baumgartner, who is the Director of Adult Congenital and Valvular Heart Disease at University Hospital Muenster and Professor of Cardiology/Adult Congenital Heart Disease at the University of Muenster, points to the changing AS population.

‘New entities such as low flow low gradient AS with preserved EF and normal flow low gradient AS with preserved EF have been proposed although it is still controversial who in these groups has severe AS and benefits from surgery,’ he told CardioPulse ahead of his presentation.