

EDITORIAL COMMENT

# Precision Medicine for Aortic Stenosis

## The Future of Cardiology Today\*



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Despite all our success in cardiology, we are still, in some ways, working at an obtuse level. We try and find individual markers for disease pathology (1), risk (2), or for triaging patients for certain therapies (3), and when that is not possible, we create small multivariable statistical models for prediction (4). That strategy has worked to some extent, especially with imaging-related markers (3), but it has also raised questions about generalizability and comparative effectiveness (4,5). In addition, this is a slow trial and error process (needing to find a precise variable or two), and the time line for success is uncertain (needing to test under multiple conditions and together with multiple variables). We also understand success of therapies at a population level, hope that therapy applies to the individual patient, and often end up practicing imprecise medicine by extrapolating therapies to the wider population. This is well beyond the trial enrollment criteria or base therapies on triage variables that are themselves imprecise (e.g., triaging for implantable cardioverter-defibrillators in dilated cardiomyopathy based on ejection fraction [EF] alone).

What can hasten the process of discovery and help in precise targeting of therapies to reliably modify outcome? Perhaps a finer understanding of diseases and a major redirection of strategy using large-scale multidisciplinary analytical methods of detecting critical variables or association of variables could immensely speed up this journey of discovery? A better understanding of disease as the basis of

rational treatment has been pivotal to the success of modern medicine and will probably reach its zenith in personalized medicine—when signature characteristics can be identified at an individual person or group level that strongly dictates therapy and outcomes. However, many diseases are complex, and outcomes are dependent on a plethora of factors; identifying such precise disease- and person-based signatures is a function of how well we can stratify human disease into ever increasingly finer hierarchical structures. For example, physicians have long understood that diabetes mellitus has 2 major subtypes with distinct molecular etiologies: type 1 and type 2. Understanding the difference between these 2 forms of diabetes was a breakthrough because they require different treatment strategies and are associated with different outcomes. The algorithm for delineating between type 1 and type 2 diabetes requires only a single data point: is this form of diabetes sensitive to insulin (type 1) or not (type 2)? Thus, if we define precision medicine as use of data to stratify disease into distinct subtypes learned from data, then physicians already use a precision approach to medicine.

However, what if a single data point is not enough? The stratification of chronic, complex disease using these simple, expert-derived algorithmic approaches is often not wholly adequate. To continue with the example of diabetes, it was recently demonstrated that type 2 diabetes is not simply a monolithic disease characterized by resistance to insulin, but instead appears to be at least 3 distinct diseases that share a number of clinical and molecular features (6). Subtypes clarified through advanced data analytics have prognostic import (7). Thus, the real premise of precision cardiovascular medicine is that we can couple advanced algorithms from the fields of computer science, machine learning, and statistics with ever-accumulating, variable-rich data sets of human disease to stratify complex disease entities into new subtypes, each of which may require differential management.

\*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *iJACC* or the American College of Cardiology.

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## PRECISION MEDICINE COMES TO AORTIC STENOSIS

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There has been an explosion of machine-learning approaches in cardiology (8) looking at diagnosis (9-12), automation of an imaging read (13), or predicting outcome (14-16). Little work has been done in valvular heart disease, especially aortic stenosis (AS) (17). An elegant and comprehensive study in this issue of *JACC* that examines an animal model and a large clinical data set rectifies this deficiency to some extent.

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In this issue, Casaclang-Verzosa et al. (18) bring the application of precision medicine to an increasingly important problem in cardiology—AS. The investigators used an elegant artificial intelligence technique called topological data analysis (TDA) to construct a network of 246 patients with AS, and then studied the topology of this network (or put more plainly, they examined patterns of how the patients in the network connected to each other) to identify subtypes of AS with higher resolution than standard clinical approaches allow. The investigators used aortic valve area, left ventricular EF, left ventricular mass index, and relative wall thickness to assemble their patient–patient network. A variety of other variables were then used to characterize the network clusters constructed from these initial 4 inputs. To assess outcomes, they examined rates of aortic valve replacement (either surgical or transcatheter), a composite major adverse cardiovascular or cerebrovascular events (MACCEs), and time to first MACCE hospitalization from the index echocardiographic examination. The investigators also analyzed a large murine cohort of serially imaged animals (imaged at 3, 6, 9, and 12 weeks), which they used to better understand their human findings in relation to the findings in the longitudinal animal cohort. Incorporating animal model studies into primary research findings from human cohorts is currently not common in most clinical precision medicine research. Follow-up studies should seek to emulate this excellent idea when applicable and feasible.

The most novel and important findings of this precision approach to AS was the identification of 2 distinct pathways through which mild AS was linked to severe AS. In the first pathway, mild AS progressed to severe AS primarily through valvular dysfunction with preserved EFs, whereas in the second pathway, the progression to severe AS occurred with an accelerated decline in EFs, whereas valvular stenosis was

largely preserved. Aortic valve replacement seemed to move the patients toward the mild and moderate AS cluster zone, which suggested that the technique was dynamically responsive to changed conditions. These were intriguing findings because the discovery of different disease trajectories implied that there might be different molecular or pathophysiological bases. If further work could determine distinct molecular features that characterize these 2 pathways, and if it can be shown that this typecasting has clinical implications that are targetable, we might ultimately be able to devise new treatment strategies for preventing progression of AS.

The investigators' choice to apply TDA to this data set is commendable, but some difficulties are obvious. TDA has an extensive formalized mathematical underpinning, but can ultimately distill highly heterogeneous multivariate data sets into readily interpretable relationships, such as the patient–patient network presented in the current study. Despite its power, TDA has thus far been underused in medicine compared with other forms of unsupervised machine learning (e.g., auto-encoder neural networks or advanced matrix and/or tensor factorization algorithms). The slow adoption of TDA compared with other techniques likely results, at least partially, because the pre-eminent TDA software platform from the company Ayasdi, Inc. (Menlo Park, California) is not freely available, unlike most other machine learning and artificial intelligence solutions used in academia. This is an unfortunate but largely unavoidable limitation for other researchers hoping to use TDA for precision medicine and might affect replication efforts. The absence of a validation cohort, and, more importantly, lack of serial studies to see how it maps progression of AS in humans prevent a clear understanding of how it will add to current methods of categorization of AS.

## IS AS A GOOD CANDIDATE FOR SUCH PRECISION DIAGNOSTIC APPROACHES?

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We have previously enumerated several criteria that indicate a disease will likely be amenable to a precision approach (19,20). First, diseases are primarily classified symptomatically instead of according to their etiology pathology. AS fits well here because the current clinical diagnostic approach is largely based upon the degree of symptoms and the extent of anatomical stenosis instead of the underlying molecular processes. Second, diseases are characterized by biomarkers or imaging findings that do not faithfully reveal the underlying complexity; again, the

extent of anatomical stenosis of the aortic valve and other morphological features do not fully capture the heterogeneity of the disease. Third, diseases manifest variably over an extended time frame; the variable presentation and rate of change in disease status in AS provides an axis upon which patients may be stratified and differentially treated. The investigators of this study nicely extended this third point when they addressed how patients move through the patient–patient network following aortic valve replacement.

## FUTURE STEPS

The investigators presented an innovative precision medicine approach to AS. As input variables for their TDA, they considered primarily echocardiographic

imaging findings and clinical variables. Even more precise characterization of AS in the future will doubtlessly build upon these results by including patient genetic data and perhaps data from other emerging technologies (e.g., wearable devices) and -omics data (e.g., genomics, metabolomics, proteomics, and so on). Taken altogether, we believe that this novel study points a way forward in AS. However, it also has important lessons for nearly all diseases in cardiovascular medicine.

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**KEY WORDS** aortic stenosis, left ventricular function, patient similarity, topological data analysis