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State-of-the-Art Informatics (J Singh, Section Editor)

Artificial Intelligence in Cardiovascular Medicine

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Abstract

Purpose of review The ripples of artificial intelligence are being felt in various sectors of human life. Machine learning, a subset of artificial intelligence, extracts information from large databases of information and is gaining traction in various fields of cardiology. In this review, we highlight noteworthy examples of machine learning utilization in echocardiography, nuclear cardiology, computed tomography, and magnetic resonance imaging over the past year.
Recent findings In the past year, machine learning (ML) has expanded its boundaries in cardiology with several positive results. Some studies have integrated clinical and imaging information to further augment the accuracy of these ML algorithms. All the studies mentioned in this review have clearly demonstrated superior results of ML in relation to conventional approaches for identifying obstructions or predicting major adverse events in reference to conventional approaches.
Summary As the influx of data arriving from gradually evolving technologies in health care and wearable devices continues to be more complex, ML may serve as the bridge to transcend the gap between health care and patients in the future. In order to facilitate a seamless transition between both, a few issues must be resolved for a successful implementation of ML in health care.

Introduction

Cardiovascular disease is considered one of the major health problems in the world that has claimed more lives than any form of cancers and respiratory diseases combined [1]. Multiple etiological factors, complex disease pathways, and heterogeneity in clinical presentations make cardiovascular disease detection and prognostication a daunting task. Moreover, the technological revolution with the emergence of complex high-dimensional data that results from integration of electronic medical records, mobile health devices, and imaging data poses several challenges; however, it offers newer opportunities for data-driven discovery and research. Although traditional statistical approaches for risk stratification have been developed, majority of the models show limitations in individualized risk predictions. Newer approaches using artificial intelligence (AI) and machine learning (ML), a subset of AI, have recently emerged as a potential solution for overcoming the confines of conventional inquiry [2].

Overview of artificial intelligence and machine learning

Artificial general intelligence can be referred to a general-purpose system with a capability of reasoning and *thinking* skills with wide knowledge which allow for dynamicity in intelligence in various topics and use cases that are comparable to the human mind, or perhaps beyond. Artificial applied intelligence, on the contrary, has a rather dedicated purpose that is already powering software applications and services, domotics (home automation systems), driverless cars, and natural language processing included in health care. Developments in automation and AI in the last decade have revolutionized commercial industry and have demonstrated a great sense of potential in the health care as well. AI performs a given task intelligently and adapts to disparate situations without a set of guiding rules to pilot the next steps. It rather assesses and learns from the pattern in the data that it acquires, albeit in different constructs: general and applied AI.

Machine learning (ML), a subset of artificial applied intelligence, is an umbrella term for algorithms and statistical models that equip performance improvement on specific tasks. It automates model building for extracting patterns or decision support by learning from the data. Consequently, interest in machine learning and AI has increased in the recent years to understand heterogeneity, diagnoses, and predictions in cardiovascular medicine [3]. It needs to be distinguished that the learning from ML may augment medical decision-making using features that may be unconventional and are not related to underlying pathophysiological processes [2, 4–6]. This "black-box" nature of ML algorithms has posed considerable challenges in clinical adoption and has resulted in inertia to the evolving paradigm of precision medicine in the clinical world. Therefore, there is an imperative need in health cares for assessing and standardizing machine learning techniques for their routine integration in clinical practice [2, 5].

Two of the most popular machine learning methods (Table 1) are supervised and unsupervised learning, but semi-supervised and reinforcement learning methods are also gaining traction in health care industries (Table 2) [5, 6]. The supervised learning method is trained to build a model on the sample from a select feature space derived from various imaging modalities and clinical variables along with the outcome of interest. It drives prediction and risk

Table 1. Types of machine learning

Type of machine learning	Description	Examples
Supervised learning	The dataset has labels and outcomes. The ML algorithm infers from the data which drives prediction.	There are a number of examples of supervised learning which include logistic regression, ridge regression, elastic net regression, least absolute shrinkage and selection operator (LASSO) regression, Bayesian networks, random forests, and artificial neural networks [5, 6].
Unsupervised learning	It must identify key relationships and similarities in a dataset without prior labels or annotations. Generally, the data is not divided into training and testing sets.	Prominent examples of unsupervised learning include hierarchical clustering, k-means clustering, and principal component analysis [5, 6].
Semi-supervised learning	A learning process in which the input of the data has labeled and unlabeled outcomes and classes.	It is a type of learning which includes a mixture of labeled and unlabeled outcomes and classes. It is used in image and speech recognition [5, 6].
Re-enforcement learning	Learning method based on behavioral psychology, uses reward function.	This method is based on human psychology and uses certain reward criteria. It is being used in medical imaging, disease screening, analytics, and prescription selection [5, 6].

stratification of cardiovascular diseases or classification of diastolic dysfunction from the learnt parameters, for example, that responds to the feedback based on the label from modalities such as echocardiography, cardiac magnetic resonance (CMR), cardiac computed tomography (CT), single-photon emission computed tomography (SPECT), or positron emission tomography (PET). Unsupervised learning, however, is example-agnostic and must learn the relationship from the dataset without labels or annotations to guide it.

Despite the goal of the learning algorithm or techniques applied, one must be cognizant, however, in meticulous collection and labeling (for supervised learning) of the data to prevent bias to creep into the models. For example, sampling bias can creep in if the training data does not accurately represent the heterogeneity in the cardiovascular diseases. Prejudicial bias may be introduced into the model that is induced by training the sample influenced by cultural, ethnical, or gender, and may exhibit negative impact on the patient care. Measurement bias is yet another important factor that cannot be dismissed in cardiovascular medicine. Error is introduced if the model is trained on incorrect and noisy image data or inaccurate measurements from modalities like echocardiography or cardiac magnetic resonance imaging.

A variety of machine learning and artificial intelligence techniques have been successfully studied in cardiovascular medicine in the last few years for diagnoses, classifications, predictions of mortality, cardiac hospitalizations, and major adverse cardiac and cerebrovascular events (Fig. 1a) [4]. These studies have demonstrated the potential for improved patient care and clinical

Table 2. Examples of recent studies applying machine learning technologies in cardiovascular medicine

Study	Algorithm model	Data source	Brief study description
Sengupta et al. [7]	Supervised learning	Echocardiographic data: speckle tracking	To distinguish between constrictive pericarditis and restrictive cardiomyopathy
Narula et al. [8]	Supervised learning	Echocardiographic data	To distinguish between athlete heart and hypertrophic cardiomyopathy
Tabassian et al. [9]	Supervised learning	Rest and stress echocardiographic data	To utilize machine learning during spatiotemporal variations of left ventricular strain rate during exercise and rest to identify patients with heart failure with preserved ejection fraction
Samad et al. [10••]	Supervised learning	Echocardiographic data	To predict patient outcomes and survival by using a combination of echocardiographic and clinical data
Alonso et al. [11]	Supervised learning	Myocardial perfusion data	To predict the risk of cardiac death from a combination of myocardial perfusion data and clinical information
Motwani et al. [12]	Supervised learning	Cardiac CT	To predict 5-year all-cause mortality for suspected CAD patients
Kang et al. [13]	Supervised learning	Cardiac CT	To detect obstructive and non-obstructive coronary lesions
Lancaster et al. [14•]	Unsupervised learning	Echocardiographic data	To explore natural clustering of echocardiographic variables to examine left ventricular function and identify high-risk phenotyping patterns
Betancur et al. [15•]	Deep learning	Myocardial perfusion data	To estimate the prediction of obstructive coronary artery disease
Zhang et al. [16]	Deep learning	Echocardiographic data	Utilized a deep learning algorithm to identify different echocardiographic view classes within a large sample and

Table 2. (Continued)

Study	Algorithm model	Data source	Brief study description
			achieved high level of accuracy
Zhao et al. [17]	Reinforcement learning	Patient data	To identify the ideal sequence of medications in non-small cell cancer
Madani et al. [18]	Semi-supervised learning	Echocardiographic data	Uses a semi-supervised machine learning model for left ventricular hypertrophy classification

integration [19]. Furthermore, the influx of data from electronic health records (EHR) has made natural language processing a prospect that could pay creative dividends in cardiovascular medicine for better patient outcome. The rapid data generation and collection also from various modalities and wearable devices have made data-hungry neural network models, a class of ML, an influential prospect. Recently, deep learning, a large neural network, has gained momentum in cardiology which demonstrated better performance than traditional machine learning [16]. Similarly, a novel and powerful method called generative adversarial network could model the density estimation of the data to generate new examples from its knowledge without labels or prediction ethos [20]; this can have profound implication in cardiovascular imaging such as reducing noise in low-dose CT or mere synthetic imaging data generation [20], for instance. Similar other technologies have been developed in the past years, and exciting new studies that explore the use of ML in various domains of cardiology can be relished.

Application of machine learning in echocardiography

Echocardiography is an indispensable tool for all cardiologists and is fundamental in the clinical care of cardiology. Assimilation and development of multiple echocardiographic parameters and novel techniques such as speckle-tracking and vortex flow mapping have introduced and increased the sheer number of parameters that have challenged the clinicians' ability to integrate and interpret the results [21]. Utilizing trove of information presented by ultrasound modality, many literary articles have attempted to classify, diagnose, or predict heterogeneous data such as heart failure with preserved ejection fraction [9]; create factions of phenotypic left ventricular diastolic function [14•]; or assess athlete's heart and hypertrophic cardiomyopathy [7] using ML. Noticeably, these methods produced results comparable or better than conventional methods.

Zhang et al. applied convolutional neural network (CNN), a class of deep neural network, to perform fully automated and scalable analysis pipeline for echocardiographic interpretation in a massive sample size of 14,035 echocardiograms collected over a 10-year period [16]. The CNN was trained for

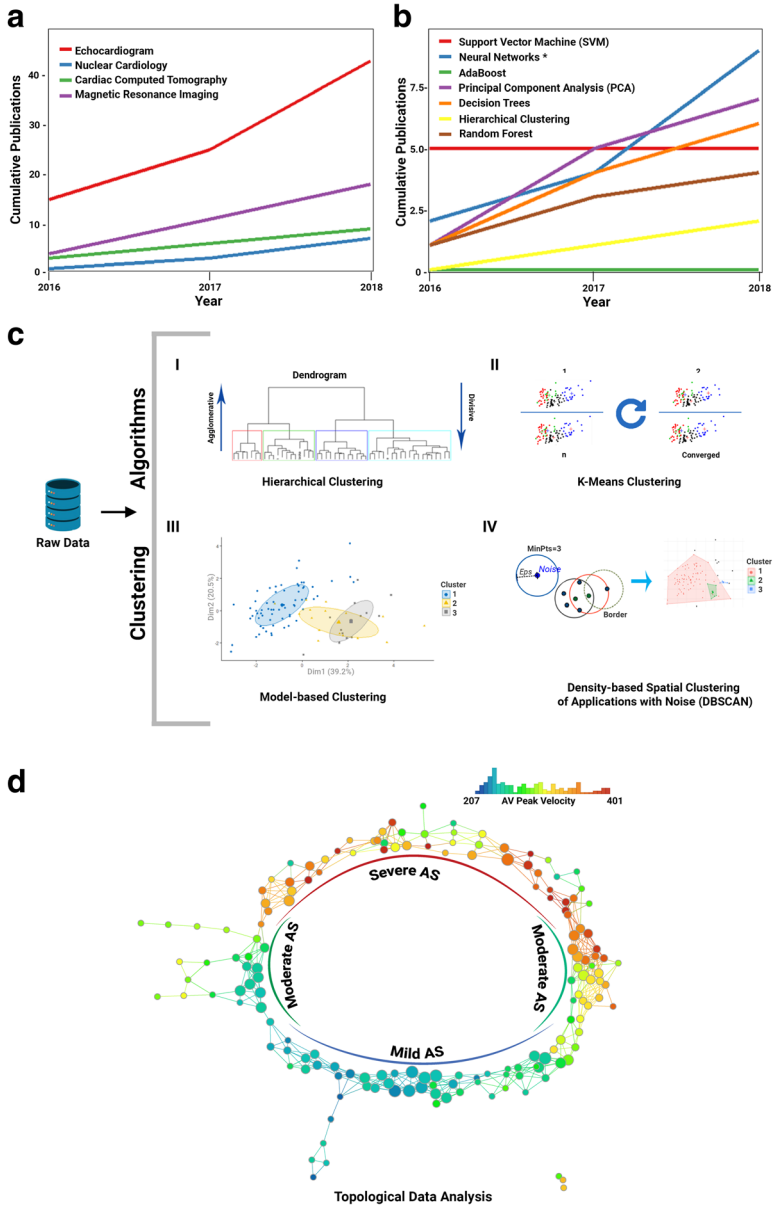

Fig. 1. Application of machine learning in cardiovascular medicine. The data was collected using R package RISmed to retrieve the publication data on cardiology imaging from PubMed between 2015 and 2018 (adapted from our previous work [2]). **a** Cumulative usage of machine learning techniques in cardiac imaging publications in various modalities. **b** Cumulative publication counts for mostly used machine learning algorithms. **c** Figures of types of clustering analysis demonstrating clusters of data (adapted from our previous work [1]). (I) Dendrogram of hierarchical cluster showing clusters of patients in each colored rectangle box. The number of clusters depends on where the dendrogram is cut. (II) Iterations of K-means clustering demonstrating the adjustments in centroids until convergence. (III) Model-based clustering considers the data comes from a mixture of density and modeled by Gaussian distribution. (IV) Algorithm considers the point based on Eps, the minimum distance between two points, and MinPts, the minimum number of points to form a region, and created the cluster according to the given criteria. **d** Topological data analysis clustering similar patients according to the severity of aortic valve stenosis. It uses a machine learning framework to create patient-patient similarity network.

identifying 23 view points and segmentation of cardiac chamber across 5 common views. Impressively, the algorithm was successful in identifying views (96% for parasternal long axis) and enabled segmentation of cardiac chambers. Furthermore, the authors demonstrated that the automatic measurements were superior to manual measurements across 11 consistency metrics like the correlation of left atrial and ventricular volumes.

Although this is encouraging, some aspects of the study must be taken with caution or require further validation. The algorithm may have correlated well with manual measurements but there were wider limits of agreement [22]. This underscores the significant variability of echocardiographic findings in daily practice, and the lack of gold standard measures like cardiac magnetic resonance imaging limits the interpretation of accuracy of the ML network. But it outlines an important milestone—the algorithmic objectivity could allow clinicians to automate measurements, data preparation, and standardization [22] while they divert their focus towards patient care.

Similarly, Samad et al. used ML to predict all-cause mortality by integrating high-dimensional echocardiographic measurements and electronic medical information in a cohort consisting of 171,510 patients [10••]. The random forest model, an ensemble learning method, was compared with the logistic regression model using a range of analytic approaches using echocardiographic and clinical variables to predict outcome. The mean area under the curve (AUC) was used to compare models and scoring systems over tenfold cross-validations. Simultaneously, this was performed over 10 survival durations from 6 to 60 months. The random forest models were able to achieve superior prediction accuracy (all AUC > 0.82) over common clinical risk scores (AUC $= 0.69$ to 0.79) and outperformed logistic regression models ($p < 0.001$) on all survival durations. However, the key distinctive feature displayed by Samad et al. was pursuing a broad initial hypothesis rather than contemporary hypothesis-driven research [2] that can help bridge knowledge gap by revising initial inquiry or give rise to brand new questions.

Application of machine learning in nuclear cardiology

Betancur et al. conducted a multi-center study assessing automatic prediction of obstructive coronary disease by myocardial perfusion imaging (MPI) [15•]. The deep learning model was trained with raw and quantitative polar maps to predict coronary artery stenosis which showed superiority to total perfusion deficit (TPD) ($p < 0.01$). Obstructive coronary disease was defined as stenosis exceeding 70% or 50% for the left main artery. The total cohort consisting of 1638 patients without known coronary artery disease underwent stress Tc-sestamibi or tetrofosmin MPI at nine different institutions with new-generation solid-state scanners. Following MPI, invasive coronary artery angiography was performed within 6 months, and the algorithm was subsequently assessed for predicting coronary artery stenosis in a tenfold stratified cross-validation procedure. Among the 1638 patients, only 1018 (62%) had obstructive coronary artery disease and only 1797 coronary vessels amid 4914 (37%) had obstructed vessel lesions. Deep learning had a higher area under the receiver operating curve than TPD for coronary disease prediction (per patient, 0.80 vs 0.78; per vessel, 0.76 vs 0.73; $p < 0.01$). Interestingly, if the deep learning

algorithm matched the TPD specificity, per-patient (79.8 to 82.3%, $p < 0.05$) and per-vessel (64.4 to 69.8%, $p < 0.01$) sensitivity increased with deep learning. Betancur et al. show that deep learning has the capability to advance automatic interpretation of MPI in relation to current approaches.

Alonso et al., on the other hand, developed a ML algorithm to approximate the risk of cardiac death derived from an amalgamation of adenosine myocardial perfusion SPECT (MPS) and clinical data which was consequently compared with logistic regression [11]. The models were exposed to 122 probable clinical predictors in 8321 patients and 551 cases of cardiac death. The ROC curve was used to measure accuracy within a cross-validation network. Interestingly, the logistic regression was outperformed by all ML approaches (AUC = 0.76; 14 features). The support vector machine (SVM) demonstrated the greatest accuracy (AUC = 0.83; $p < 0.0001$; 49 features), while the least absolute shrinkage and selection operator (LASSO) model demanded the least number of features (AUC = 0.77; $p = 0.045$; 6 features). Alonso et al. concluded that LASSO was superior to logistic regression by providing the best AUC for showing the risk of cardiac death in patients undergoing MPS.

The authors articulated and demonstrated the superiority of machine learning models to augment prognostic value from multi-dimensional MPS and clinical variables while concurrently increasing interpretability. However, this should not underscore our proclivity towards ML models over traditional statistical models, rather it assuages our decades-old consternation of inability to integrate high-dimensional data and identify motif that may otherwise be obfuscated by our perception of parameters [23].

Indeed, the high-dimensional and imaging data along with ML models like neural network could improve the efficiency and reproducibility of clinical assessment as Tan et al. demonstrated in their scholarly study of fully automated LV segmentation using neural network regression–based algorithm [24]. This was achieved by using short and long axis scans through all cardiac phases. The measurement and comparison were performed through Jaccard, dice index, modified Hausdorff distance (MHD), and blood volume. They utilized *t* test to compare with other previous databases. When testing with the left ventricular segmentation challenge (LVSC) database, they demonstrated 0.77 ± 0.11 (Jaccard index) and 1.33 ± 0.71 mm MHD. Moreover, Tan et al. tested the model with Kaggle database, a leading data science competition and database platform, for blood volume which showed $+7.2 \pm 13.0$ mL and -19.8 ± 18.8 mL for the end-systolic and end-diastolic phases, with a profound improvement ($p < 0.001$) for the end-diastolic phase demonstrating strong performance and practical clinical utility.

Application of machine learning in cardiac CT and cardiac MR

ML algorithms have been instrumental in the field of computed tomography (CT) and magnetic resonance imaging (MRI) for enabling imaging information extraction in a variety of studies. Although the volume of the studies utilizing ML in these modalities is fewer compared with that of echocardiography, however, the studies demonstrated in recent studies have shown promising solutions in the application of ML. For example, Kang et al. utilized an ML algorithm designed to detect the presence of coronary artery stenosis ≥ 25% in

CT from 42 patient datasets. Remarkably, the ML algorithm achieved high sensitivity (93%), specificity (95%), and accuracy (95%) with a ROC of 0.94 in reference to three expert readers [13]. The ML algorithm demonstrated exceptional results for the detection of obstructive and non-obstructive CAD. Similarly, Motwani et al. explored the use of ML algorithm to predict the 5-year mortality in CT in relation to conventional cardiac metrics among 10,030 patients suspected for CAD [12]. Surprisingly, the ML algorithm displayed higher AUC (0.79) than fractional flow reserve (0.61) or CT severity scores (SSS = 0.64, SIS = 0.64, DI = 0.62) for predicting the 5-year all-cause mortality with a significant difference ($p < 0.001$). Similarly, Rosandael et al. investigated the use of ML algorithm to predict major cardiovascular events using only CT variables in 8844 patients in comparison to CT severity scores for suspected CAD patients [25]. Notably, the AUC for the ML algorithm (0.77) was superior to CT severity scores (0.68–0.70) with a remarkable difference ($p < 0.001$) for anticipating major cardiovascular events.

Similarly, in the recent years, the interest in the application of ML in cardiac magnetic resonance imaging has piqued. Winther et al. utilized a deep learning approach for automatic segmentation of the right ventricular and left ventricular endocardium and epicardium for calculating cardiac mass and function parameters from a number of datasets [26]. The ML algorithm achieved comparable or higher outcomes in relation to human experts. The findings were limited due to small sample sizes. Tan et al. utilized a convolutional neural approach for automatic left ventricular segmentation in all short axis slices and phases in publicly available datasets [27]. They obtained a Jaccard index of 0.77 in the left ventricular segmentation challenge dataset and continuous ranked probability score of 0.0124 with the Kaggle second annual data science bowl. Tan et al. showed the effectiveness of ML algorithm in automatic left ventricular segmentation.

Application of machine learning for detecting cardiac disease phenotypes

Cardiovascular disease is a heterogeneous disease that impacts the patients of disparate socioeconomic and pathophysiologic backgrounds. Diverse patient groups may not respond well to a generic treatment. Comprehending data from such diverse groups of patients has proven to be challenging, and phenomapping may provide assuage to such challenges by utilizing vast amounts of data for classifying through types, as traditionally used in DNA analysis. However, the method has also extended the scope in imaging data and expanded the spectrum of ML use in various cardiovascular disease phenomapping. For example, Tabassian et al. utilized ML to analyze the timing and amplitude of the LV long axis myocardial motion and deformation during stress and rest [9]. This was subsequently compared with traditional measurements in patients with heart failure with preserved ejection fraction (HFpEF), healthy, breathless, and hypertensive in 100 prospectively recruited subjects. Tabassian et al. extracted velocity, strain, and strain rate curves from all 18 segments of the LV during rest and submaximal exercise testing. Subsequently, the ML model was used to segregate phenotypic relationships for diagnosing

the HFpEF. The learnt strain rate parameters provided utmost accuracy for assigning subjects into four groups (overall, 57%; HFpEF patients, 81%) and into two classes (asymptomatic vs symptomatic; AUC = 0.89; accuracy = 85%; sensitivity = 86%, specificity = 82%). When comparing ML with conventional measurement for strain, it showcased the highest improvement in accuracy for the two-class task (+ 23%, $p < 0.001$), comparison with + 11% ($p < 0.001$) using velocity, and + 4% ($p < 0.05$) using strain. Tabassian et al. concluded that ML can be leveraged to identify spatiotemporal variations within LV during rest and exercise in HFpEF to provide a standard for diagnostic classification.

While Tabassian et al. have performed exemplary work, many factors need to be addressed [7]. Tabassian encountered an enigma within their data which consisted of 36 segmental curves for each patient with 208 and 123 time points at rest and exercise, respectively. They used unsupervised learning to break down the complexity of the data into reduced dimensions. It is a method to represent data in less features, potentially to reduce noise and multicollinearity, from a high-dimensional data obtained from imaging modalities and clinical data. Subsequently, they used a supervised classification algorithm to categorize patients into one of four groups. Though innovative in approach, this can potentially compromise the model's efficacy and relatability to the real world [7] since a small sample size may not capture the heterogeneous nature of HFpEF and data imputation method may introduce errors that may not be indicative of the patient population.

Clustering approaches and patient similarity

Clustering is an unsupervised learning task that identifies inherent factions from the data with the homogeneous group that the algorithm learns from the pattern (Fig. 1b) [28]. It may be useful in identifying phenotypes or segment patients according to the diseases and conditions as Sanchez-Martinez et al. described in their study of HFpEF patients [29]. Sanchez-Martinez et al. evaluated measurement of LV function at rest and exercise to examine differences between HFpEF and healthy patients [29]. They utilized data derived from the MEDIA (metabolic road to diastolic heart failure) study and examined 156 patients ≥ 60 years subjected to stress echocardiography. An unsupervised ML algorithm was used to assemble patients according to similarity which enabled examination of velocity patterns, and clinical validation was successively performed. The correlation with diagnosis was noteworthy (κ, 72.6%; 95% confidence interval, 58.1–87.0). Next, the algorithm was tested on 51 additional subjects. Interestingly, it classified 33% of hypertensive and 67% of breathless controls as mild HFpEF. In conjunction with the examination of LV long axis function during exercise, ML may provide valuable insight into HFpEF mechanisms.

Several unique explorations using ML were contributed in heart failure like Tabassian et al. and Sanchez-Martinez et al. had. Lancaster et al. proposed a clustering framework for echocardiographic variables to evaluate LV dysfunction for high-risk phenotypic patterns and prognostic significance [14•]. The clustering algorithm was used in 866 consecutive patients. The major adverse cardiovascular events, mortality, and hospitalizations were compared with cluster- and traditional-based classifications. The clustering mechanism

subsequently isolated diastolic dysfunction in 559 of 866 patients and identified two distinct groups. This revealed moderate agreement with conventional classification (kappa = 0.41; $p < 0.0001$). Further cluster analysis was performed in 387 patients to categorize the severity of diastolic dysfunction into two groups. It revealed a good agreement with the traditional classification (kappa = 0.619; $p < 0.001$) that demonstrated the capability of algorithmic objectivity to recognize patient groups with similar risk and potentially improve clinical risk and outcome prediction.

A novel state-of-the-art technique to generate patient similarity network called topological data analysis (TDA) uses clustering in unsupervised applications to build network and shape that describe the data [30] (Fig. 1c). The TDA method has been applied previously in other scientific fields of oncology, genomics, diabetes, and preclinical spinal cord injury, for example [30–38]. In their erudite work, Casaclang-Verzosa and colleagues astutely applied TDA to discern patient similarity for precise phenotypic recognition of the pattern of LV responses during the progression of aortic stenosis (AS) [39••]. The patient similarity network formed a loop in which the algorithm mechanistically segregated patients with mild and severe AS ($p < 0.001$) on the left and right side but linked through moderate AS on the top and bottom sides of the loop with reduced and preserved ejection fraction ($p < 0.001$). The data tested on the patients with aortic valve replacement, following their initial assessment, showed their recovery from the severe region to the mild or moderate region of the loop. As a reverse translational study, the network was validated against the mice data which also showed similar distribution with segregated higher and lower peak aortic velocities ($p < 0.001$).

Our views on machine learning

Contemporary progress and studies in ML and cardiovascular medicine have been driven by a few main reasons. First, development and increments in imaging parameters, EHR, and mobile solutions have increased the availability of valuable datasets that may encompass the heterogeneity of the diseases. Second is the development of new and sophisticated learning algorithms and exploratory methods to integrate high-dimensional data and expose underlying patterns and perceptions of the diseases or conditions. Third is the emergence and acceptance of cloud computing providing low-cost and portable solutions to sophisticated data mining and analytics. The sheer volume and velocity of the data adjure ML solutions for scalable procedures and perform computational and statistical solutions rapidly. Yet, cardiovascular medicine is not only resolute in veracity and the prediction of outcomes but also to customize the requirements based on the circumstances of individuals for the feasibility of precision cardiology.

Several new methods and tools have emerged to encourage and simplify precision medicine utilizing a standard platform for genomic data [38]. These tools are created in collaborations with health care organizations and industries to create actionable insights from omics data. Similar collaborations are also being spearheaded and explored between American Heart Association's Institute for Precision Cardiovascular Medicine, industries, and institutions to utilize machine learning for actionable insights and precision cardiology. It is

undeniable that there are opportunities and potential in machine learning and artificial intelligence to ascertain novel insights in cardiovascular diseases and conditions, but the collaborations and shared insights between organizations may simplify the process, intuition, and cognizance easier to access. The advent of ML has fundamentally shifted the paradigm for conventional thinking in research, but encouraging spectrum of approaches in utilizing it and sharing ideas could bridge a gap or deficiency in knowledge [2].

In the dynamic era of data explosion and collection, traditional tenets of statistical evaluation must also evolve. Restricting the exploration to predictors obtained from uncertainty principles of statistics in prediction-driven innovative algorithm is unlikely to ameliorate scientific exploration. It must be robust and vigorous, but it must also inspire adaptive cognitive quest. The principal virtue of AI and ML is beneficence through decision support, intelligence, and risk mitigation in the quest of adaptive reasoning. It is vital to leverage the knowledge representation and automated reasoning in cardiovascular medicine, but justly is essential to evaluate ethical, legal, and social implications and develop a set of guidelines and standards [23].

Compliance with Ethical Standards

Conflict of Interest
Karthik Seetharam and Sirish Shrestha each declare no potential conflicts of interest.
Partho P. Sengupta is a consultant for HeartSciences and Ultromics.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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39.•• Casaclang-Verzosa G, Shrestha S, Khalil M, Cho JS, Tokodi M, Balla S, et al. Network tomography for understanding phenotypic presentations in aortic stenosis. JACC Cardiovasc Imaging 2019 (in press). This is the first study in diagnostic clinical cardiology to demonstrate effective use of patient similarity network.
This study uses a novel technique called topological data analysis for the first time in cardiovascular disease. It demonstrates a unique and important method in grouping patients with similar presentation of aortic stenosis while capturing the notion of progression in the disease.

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