Review

Journal of Cardiovascular Pharmacology and Therapeutics
1-12

DOI: 10.1177/1074248420928651
journals.sagepub.com/home/cpt
SAGE

# Machine Learning in Cardiology—Ensuring Clinical Impact Lives Up to the Hype

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**Abstract**

Despite substantial advances in the study, treatment, and prevention of cardiovascular disease, numerous challenges relating to optimally screening, diagnosing, and managing patients remain. Simultaneous improvements in computing power, data storage, and data analytics have led to the development of new techniques to address these challenges. One powerful tool to this end is machine learning (ML), which aims to algorithmically identify and represent structure within data. Machine learning's ability to efficiently analyze large and highly complex data sets make it a desirable investigative approach in modern biomedical research. Despite this potential and enormous public and private sector investment, few prospective studies have demonstrated improved clinical outcomes from this technology. This is particularly true in cardiology, despite its emphasis on objective, data-driven results. This threatens to stifle ML's growth and use in mainstream medicine. We outline the current state of ML in cardiology and outline methods through which impactful and sustainable ML research can occur. Following these steps can ensure ML reaches its potential as a transformative technology in medicine.

**Keywords**

cardiology, cardiovascular disease, machine learning, artificial intelligence, deep learning

## Machine Learning in Cardiology—Where Are We Today?

In the past 3 decades, each of the 6 major pillars of cardiovascular medicine—cardiac electrophysiology, heart failure and transplantation, advanced cardiac imaging, structural and interventional cardiology, congenital cardiology, and preventive cardiology—have experienced monumental clinical and basic science advances that have significantly reduced morbidity and mortality for millions of patients.[1-6] Despite these advancements, enormous challenges in each of these fields remain.

In electrophysiology, pioneering atrial fibrillation (AF) ablation techniques such as pulmonary vein isolation,[7-10] mitral isthmus ablation,[11] and the development of pulse field ablation[12] have reduced morbidity for patients with AF. Safer yet more efficacious novel anticoagulants including factor Xa[13-15] and direct thrombin inhibitors[16] have reached the market, helping to prevent arrhythmogenic stroke. However, some project the prevalence of AF will double by 2030 and triple by 2050,[15,17,18] AF-related stroke risk changes rapidly,[19] and identifying patients who have subclinical AF remains a challenge.

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**Manuscript submitted:** March 15, 2020; **accepted:** May 3, 2020.

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In heart failure, a better understanding of cardiac pathophysiology has led to a more comprehensive and straightforward treatment regimen aimed at both reducing cardiac remodeling[20] and emphasizing neurohormonal blockade[21-24] in patients with reduced ejection fraction heart failure. Notable improvements in left ventricular assist device technology such as the advent of continuous,[25] fully magnetically levitated centrifugal-flow machines[26] have revolutionized advanced heart failure management by reducing rates of both disabling stroke and reoperation for device malfunction. Nevertheless, preserved ejection fraction heart failure (HFpEF) research has not yet been as fruitful. Though recent breakthroughs have begun to shed light on this highly heterogeneous disease,[27] no pharmacologic agents have been shown in large clinical trials to significantly decrease mortality.[28-32] In imaging, cardiac magnetic resonance imaging has led to improved recognition of viable myocardium in the setting of previous coronary ischemia[33] but challenges remain with regard to making these advanced imaging modalities readily accessible to patients in rural areas. Additionally, echocardiography continues to suffer from user variability, and suboptimal windows often negatively impact ejection fraction and longitudinal strain estimation.

Structural and interventional cardiology has witnessed the development of effective, yet less-invasive valvular repair methods. These techniques, including transcatheter aortic valve replacement (TAVR)[3,34,35] and transcatheter mitral valve repair,[36] have significantly increased access to care for previously ineligible patients while simultaneously reducing morbidity and mortality for thousands of individuals. Moreover, the development of novel drug-eluting stents has reduced the risk of stent restenosis and subsequent acute coronary syndrome (ACS) in high-risk patients.[37,38] Despite these efforts, however, cardiovascular disease (CVD) remains the leading cause of death in the United States and worldwide; health-care expenditure for CVD diagnosis and both acute and chronic therapeutic management represent an enormous burden to reducing health-care expenses[39,40]; and clinicians and researchers continue to experience challenges in optimally screening, diagnosing, and treating patients in all cardiovascular subspecialties.[41-47]

Although these enormous barriers exist, new paths are emerging to tackle them. Improvements in computing power and accessibility through methods such as cloud computing have coincided with more streamlined electronic medical software.[48] Some of the byproducts of these developments include enhanced connectivity among data types as well as better database and file formats for data storage and analysis, encrypted cloud storage, and the development of more robust techniques to analyze large data sets.[49-51] At the forefront of these technological advancements is machine learning (ML). The primary focus of ML is to algorithmically represent structure present within data or to make predictions or classifications of outcomes based upon relationships present within that data.[52] This is particularly useful in situations where traditional statistical methods have difficulty incorporating large numbers of variables or modeling complex relationships between variables, especially when data sets are large and diverse, or variables have nonindependent relationships. Machine learning has garnered attention both in popular culture and from the medical community, and both public and private entities around the globe have taken notice. The consulting firm Accenture projects monumental investments in biomedical ML will occur over the next few years, with spending projected to reach over 6.5 billion dollars per year by 2021, an 11-fold increase in per-year spending from 2014 (https://www.accenture.com/fi-en/insight-artificial-intelligence-healthcare).

The enormous investment may be worth it. Accenture also projects artificial intelligence [AI] to save the health-care industry as much as 150 billion dollars by 2026. Furthermore, when combined with recent breakthroughs in high-resolution medical imaging such as spatial partitioning and super-resolution imaging, robust genome sequence analyses, and more accurate longitudinal measurement of physiologic metrics including the use of wearable devices, ML has demonstrated significant breakthroughs in various basic science and clinical research settings. As Topol has discussed,[53] the past few years of ML-related research alone have yielded algorithms shown to accurately characterize vertebral compression fractures,[54] tuberculosis lung lesions,[55] and lung nodules[56] on imaging studies. Machine learning has also been used successfully to identify skin cancer,[57] characterize high-risk polyps on colonoscopy,[58,59] accurately visualize breast cancer on mammograms,[60,61] and even predict with high fidelity the likelihood of hypoglycemia in patients based principally on telemetry tracings.[62]

Despite enormous investment and interest, however, ML has yet to reach its potential,[63] particularly in cardiology. Although research publications related to ML have skyrocketed over the past few years, prospective studies demonstrating clinical impact, particularly in cardiovascular medicine, remain few and far between.[64] Clinical guidelines for cardiology, which physicians use on a routine basis to treat patients, barely mention ML and virtually no findings from ML projects have been incorporated into these guidelines to-date.

In this article, we explore how ML can play an instrumental role in assisting researchers and clinicians to better understand the complex pathophysiologic mechanisms of cardiovascular medicine and outline how we as clinicians and researchers can optimally utilize ML to positively impact patient outcomes in a clinically meaningful way. Finally, we provide commentary on how ML can become more mainstream for clinicians and patients as well as more sustainable for robust research moving forward.

## Machine Learning and Cardiology

Simply put, ML is the field of study concerned with algorithms that learn from data. There exists an extensive amount of software, tools, and packages that implement ML algorithms in various programming languages, many of them open-source.[65] The intricacies involved in designing ML algorithms and their respective strengths and limitations are beyond the scope of this article but can be found in many other sources.[66-70] For the purpose of this article, we will focus on 2 subcategories of ML, specifically supervised and unsupervised learning, which differ in their primary goal. In supervised learning, an algorithm is trained to predict some outcome that is specifically defined, which helps "supervise" the model's training and predictions. Here, the algorithm learns how to identify complex relationships and patterns within data, often based upon nonlinear combinations of features, and is subsequently able to make conclusions, such as predicting values or classes. These algorithms are typically built, refined, and tested on separate chunks of the data to prevent overfitting and better assess generalizability. A real-world example is when social media platforms use images labeled as a certain individual to teach a computer to identify that individual in subsequent photos. In clinical medicine, this is similar to breaking an imaging down into features (pixels) which are fed to a computer with associated labels (such as cancer diagnosis) to learn patterns that are subsequently tested on new images for automated detection.[71] In unsupervised learning, a computer again learns complex relationships within the inherent structure of data, typically without reference to any outcome (termed "label" in ML) such as "case" or "control." The ultimate hope is that the patterns or structures identified can be useful for tasks such as clustering, which can offer further insight into patient stratification within a disease. Deep learning, a class of ML that involves multiple, or "deeper," layers of abstraction, includes powerful architectures such as convolutional neural networks which have revolutionized the field of computer vision,[72] among others, and is actively being applied in the health-care field.[73] Deep learning methods, such as autoencoders, involve a combination of unsupervised learning with a supervised learning method "stacked" on the final layers of the model. The unsupervised component learns useful features in the data, and then the supervised model uses the learned features to make predictions.

Independent of ML technique development and refinement, health-care utilization has continued to rise.[74] As patients visit clinicians more often, they also undergo more thorough screening and more frequent diagnostic testing.[75] Every patient encounter, blood test, vital sign, and imaging study represents more useable data. In particular, cardiology represents a uniquely data-rich field,[52] where randomized controlled trials are commonplace and there is a wealth of data which may be used to objectively drive patient care. Furthermore, since most CVDs are highly chronic conditions, the longitudinal aspect of disease creates a wealth of semistructured data even in routine conditions. When these factors are combined with an aging population and increasing rates of comorbidities such as hypertension, diabetes, hyperlipidemia, cardiac arrhythmias, and heart failure,[39,40] it is clear that cardiology represents a well-positioned field for impactful ML application. Cardiovascular disease is also highly complex, and ML-based risk scoring can better capture the multidimensionality of cardiovascular pathogenesis to better predict prognosis as compared to risk-scoring systems based on standard statistical modeling.[52] Despite this, cardiology has lagged behind other medical specialties in ML-related clinically relevant research output, and very few prospective studies utilizing ML have been published in or reflected upon clinical guidelines.

## Methods for Moving the Needle on Clinical Outcomes

Despite ML's enormous potential, researchers and clinical practitioners have yet to demonstrate the clinical outcomes improvement that health-care institutions and patients seek.[63] The medical community must remain aware of the so-called "AI chasm," which refers to the substantial difference between developing a highly accurate algorithm and being able to successfully apply that algorithm in clinical workflows.[76] After all, a highly accurate algorithm is of little use without demonstrated clinical outcome improvement. This issue is highly complex and multifactorial in nature. However, there are a few steps researchers can take to make CVD-related ML research more clinically impactful.

## The Importance of a Pertinent Clinical Question and Multidisciplinary Team

The clinical question provides the basis for study design, implementation, and outcomes, and its generation represents an essential step in clinical research. Biomedical ML research is no exception. Though ML capabilities have increased dramatically over the past few years, so too have ML research articles which either do not broach a clinically relevant topic or are too challenging to generalize and apply in the confines of current clinical practice.[77] In current biomedical ML, studies appear to be driven more by data availability than by clinical relevance. Beginning the process by first identifying important, unsolved clinical questions and then examining the available data, rather than vice versa, may help to increase the clinical relevance and impact of ML results. Further, an outline for addressing an ML algorithm's potential results within current clinical medicine practice structure is essential and should be discussed prior to algorithm generation. Additionally, incorporating a multidisciplinary clinical research team across computational, biological, and medical areas of expertise is essential. Not only can such practice result in more computationally sound and clinically useful conclusions,[78] it can streamline outcomes implementation within existing institutional workflows.

This is perhaps more essential in cardiology, where there is often a plethora of data, numerous unanswered clinical questions, and the need for multiple subspecialty involvement when generating sound treatment plans for medically complex patients. For example, patients with severe aortic valvular stenosis undergoing transcatheter aortic valve intervention (TAVI) commonly suffer from atrioventricular (AV) nodal blockade intra- or periprocedurally in part as a result of mechanical impingement of the nearby AV node.[79-81] Cardiovascular interventionalists and electrophysiologists often work in lockstep to treat affected patients, with the common goal of promoting safe cardiac conduction while preserving the integrity of the newly placed valve. Transcatheter aortic valve intervention is a relatively new but now commonly utilized, safe, and highly efficacious technique used to treat a very prevalent disorder with high associated morbidity. It does, however, have a specific, potentially serious adverse effect, representing a fruitful area of potential clinical research. Since most patients undergoing this procedure receive similar preprocedural labs, imaging studies, and other associated workup, TAVI-related complications represent a worthwhile area for ML-related clinical research. To begin, retrospective data can be analyzed to develop an ML algorithm with superior risk stratification compared to traditional statistics, and that algorithm can be subsequently applied prospectively to determine whether clinical impact benefits from algorithm implementation in the everyday clinical setting. A multidisciplinary research team can additionally brainstorm the full implementation of the ML algorithm into clinical practice. This can occur through the institutional electronic health record (EHR) to facilitate streamlined risk stratification prior to every TAVI procedure and prepare contingency plans if needed. Embedding such ML work into hospital operations can enable a learning health system where past decisions can inform current ones,[82] particularly for medically complex patients.

## Data Set Generation and Interoperability

One major obstacle in the production of fruitful ML-based cardiology clinical research are the data often employed to train algorithms. Machine learning results are limited heavily by several important aspects of the underlying data, such as suboptimal quality as well as when it is cluttered, incomplete, poorly organized, not representative of the global population, or contains systematic bias, among others. In these scenarios, ML algorithms can underperform compared to standard statistical methods.[83] Missing or unknown potentially important variables can have devastating effects to the training of ML algorithms, and inaccurate data input and biased data selection can mislead an ML algorithm to make erroneous conclusions.[84] For instance, issues with algorithms used in Amazon's employee hiring were shown to be biased against female applicants at least in part due to the development of the algorithm based on 10 years of predominantly male hires.[85] Within health care, there is potential for inadvertent bias introduction within the EHR system,[86] and a recent article found evidence of racial bias within an algorithm used to identify patients with complex care needs for additional assistance programs.[87] Data issues are especially prevalent in high-volume cardiac care centers, where a wide range of advanced testing is offered to patients. Cardiology patients in tertiary and quaternary care centers generate a plethora of data from both cardiology-specific imaging modalities (electrocardiograms [EKG] and telemetry, transthoracic and transesophageal echocardiograms, cardiac magnetic resonance imaging [MRI], computed tomography coronaries) and traditional data gathered from cardiac workups in hospitalized patients (vital signs and laboratory studies, among others). Keeping well-organized and complete metrics on patients with ACS, heart failure, recent heart transplantation, cardiac conduction abnormalities, and those undergoing procedures would improve the applicability and reduce bias in ML algorithms.

Though storage capacity has increased dramatically over the past few years, data interconnectivity and harmonization remain an enormous challenge. Centers utilizing the same EHR system are often unable to store data in a manner that is accessible to clinicians and researchers in a swift and dissectible manner, and patient privacy laws limit centralization of all data across a wide number of care centers.[88] The plethora of data silos within clinical medicine—EHRs, picture archiving and communication systems from multiple vendors—separate systems for data generated from EKGs, electroencephalograms, echocardiographic imaging, and so on, and render data interconnectivity especially difficult. Open source models, which encourage open collaboration and peer production, can help facilitate reproducibility of studies and external validation, but despite this, disparate formats and data sources remain barriers to interoperability and successfully reproducing results.

One solution is the implementation of supplemental ML frameworks into cloud-based platforms such as the Amazon Web Services and the American Heart Association-powered Precision Medicine Platform (https://precision.heart.org/). This would provide optimization of imaging processing tools by quickly integrating findings from novel imaging sets. This becomes especially important as current imaging modalities continually make technical improvements.

Another strategy for increasing data harmonization is the development and implementation of a common data model system, in which models developed at one institution can be shared and easily implemented at another, thereby reducing the time and cost to replicate studies and enabling model validation without the exchange of patient data.[89] For example, the Observational Health Data Science and Informatics program has created a common data model as part of the Observational Medical Outcomes Partnership (OMOP) that was used to show the power of large-scale multi-institutional observational research. In OMOP, a variety of disparate clinical data streams are mapped to an internal system of standardized vocabularies and ontologies. This has facilitated much easier multi-institutional studies as well as replication efforts, as demonstrated by a recent slew of powerful and innovative research using such models. For example, using a subset of the over 50 databases containing over 600 million patient records, treatment trajectories for patients with type 2 diabetes mellitus, hypertension, and depression were evaluated over a period of 11 years in 4 countries.[90] In cardiology, the standardization of data sets to OMOP allowed the authors of the Large-Scale Evidence Generation and Evaluation across a Network of Databases (LEGEND-HTN) study to compare antihypertensive drug treatments for 4.9 million patients across 9 observational databases.[91] The largest of its kind to date, the study was able to evaluate the effectiveness and safety of many drugs at scale while mitigating internal bias from individual sites.[91] In addition to better facilitating replication efforts, harmonized data structures can enable other large-scale study frameworks, such as federated learning, where models built on one site can be refined using data for another, thereby making them more generalizable.[92]

## Applying ML Principles in Cardiac Pharmacology

Among the most powerful applications of ML in cardiology is the ability to tailor pharmacotherapies administered to patients with CVD and optimize individual response. As multi-omics approaches become more common, understanding patient-specific pharmacologic regimens may become more mainstream.[93] By applying the principles outlined in this article, clinicians and researchers can work hand in hand to tailor pharmacotherapies and further improve cardiovascular clinical outcomes. As an example, one relevant clinical question pertains to better elucidating the variability of patient response to different antihypertensive drugs. A multidisciplinary team, consisting of both computational and clinical experts, can develop a research framework to study this question and produce results that may be widely applicable for both researchers investigating the pathophysiologic understanding of hypertension and clinicians who are treating affected patients on the front lines. Data sets can be generated from multiple medical centers incorporating wide-ranging clinical and genomic data in a common structure that may serve as a model for other similar research endeavors moving forward. Utilizing this foundation, ML algorithms can be used to uncover optimal drug regimens and treatment doses for a given individual and identify which genetic, transcriptomic, or other patient-specific factors contribute to the variability of success seen with different drug regimens. Communicating these results in a clear and concise way, so individuals from multiple disciplines can digest findings would also serve to enhance the implementation of these discoveries into clinical and institutional workflows.

Additionally, efforts utilizing ML for drug discovery[94] or repurposing[95] have paved the way for more streamlined therapeutic agent development that is both efficacious and cost-effective. As a recent study noted, the current standard in drug development is extremely costly, and the clinical success probability for bringing a drug through phase 1 to approval was estimated to be less than 12%.[96] Machine learning can alleviate some amount of risk associated with these endeavors by automating the selection of compounds with optimal properties and promising molecular structures[97] faster and more accurate. Additionally, the process of evaluating a library of either previously approved drugs or those drugs currently in trials for application toward a new indication is a quintessential feature of drug repositioning. This is often a very tedious process, and ML-based feature engineering can be applied to identify chemical information that would be useful to prioritize for clinical investigation.[98] These principles can be applied to develop or reposition drugs to more optimally treat CVD.

## Developing a Path for Supporting Safe but Impactful Innovation

An important consideration for the production of clinically impactful ML-based cardiology research is Food and Drug Administration (FDA) approval of products. This subject has received insufficient attention from the biomedical ML community to date. By definition, Software as a Medical Device (SaMD) is any software that is intended for medical purposes such as diagnosis, prevention, monitoring, or treatment of a disease, injury, or physiological process.[99] Machine learning-based technologies fall under regulations of SaMD and therefore must provide evidence supporting a valid clinical use case as well as both analytical and clinical validation.[100] This 3-part evaluation examines whether (1) there is a valid clinical association between the SaMD output and the target clinical condition; (2) the SaMD correctly processes input data to generate an accurate, reliable, and precise output; and (3) this output achieves the intended purpose in the target population in the context of clinical care. This rigorous regulatory process is meant to ensure the safety of patients and the effectiveness of the tools, thereby promoting public trust and sustainability of SaMD. By designating SaMDs their own regulatory pathway, the FDA has provided specific guidance documents and a clear path to approval. Based on our search (see Supplemental Materials), since the FDA began approving AI-based technologies in 2014, there have been 16 cardiology SaMDs approved, with applications in arrhythmia detection and EKG using smart phones[101] or smart watches[102] to detection of ventricle function from MRIs (Figure 1).

It should also be noted that SaMDs (and to some extent, FDA approvals) will likely require industry investment and thus reliable financial incentives for development of the technology at hand. This idea is somewhat analogous to the process of commercialization of pharmaceuticals—although many discoveries leading to new medications begin in academia, the onerous process of furthering drug development, obtaining regulatory approval, and marketing the compound near-universally requires commercial partners. There is little reason to believe that the development and marketing of AI-enabled products will follow any different path. Indeed, the high ratio of publications to products suggests this is the case.[64] Missing in many AI publications to date are thorough consideration of how such a product may be marketed and used in the clinical setting. For example, consider the case of EHR-based predictive algorithms. Generally, this type of academic work has focused upon extracting, cleaning, and utilizing EHRs to build predictive models. This process is likely not portable between different institutions or EHR vendors due to the inherent complexity of hospital and medical system IT infrastructure. Furthermore, there exists little academic work demonstrating how real EHR data streams may be accessed or adapted with industry standard practices for database technologies and

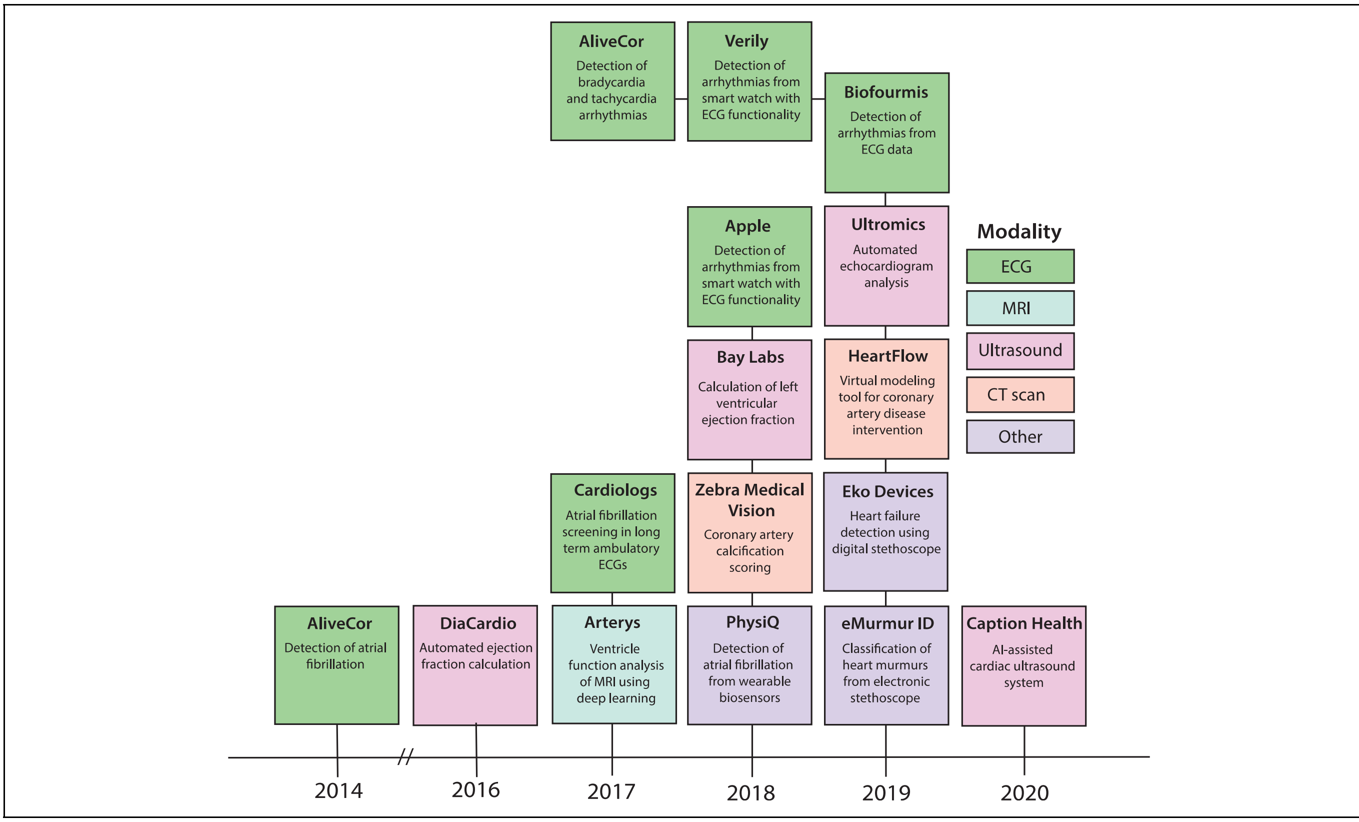


**Figure 1.** Food and Drug Administration approval of AI-based technologies in cardiology. The FDA has cleared several AI-based medical devices in cardiology that perform tasks such as arrhythmia detection and analysis of heart mechanics. These technologies utilize a variety of data modalities, including ECG recordings, imaging studies, and wearable sensor data. See Supplemental Materials for information on how these data were compiled. AI indicates artificial intelligence; FDA, Food and Drug Administration; ECG, electrocardiogram.

information security. Finally, little work to date has considered how such predictive models will be presented to clinicians and effectively adopted into clinical workflows. In many cases, these present important and unresolved problems for the clinical implementation of ML algorithms.

## The Path to Prospective Investigation

Despite the relative lack of cardiology-related ML algorithms currently deployed in practice, there are a number of studies that set the stage for more prospective investigations and could lead to integration into the clinic. In CVD prevention, an ML-based model was built to accurately identify patients who could benefit from statin therapy from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort.[103] In a subsequent study, Johnson et al retrospectively applied an ML algorithm to predict atherosclerotic plaque responsiveness to rosuvastatin therapy as measured by optical coherence tomography,[104] which could indicate a path forward to precision-based pharmacotherapy for patients with CVD. In heart failure, ML has been used to subtype HFpEF,[27] and ML-based technology has been shown to accurately assess transthoracic echocardiography results.[51,105] In cardiovascular imaging, Doeberitz et al utilized a deep learning ML framework to calculate coronary computed tomography angiogram-derived fractional flow reserve in attempts to more accurately predict future ACS within 3 years as compared to stenosis grading alone.[106] The ML algorithms have also been used in TAVR assessment by retrospectively predicting overall inhospital mortality in patients with TAVR .[107] Perhaps the most notable achievements with ML in cardiology have surrounded cardiac electrophysiology, in which algorithms have been developed to predict subclinical paroxysmal AF in patients with normal sinus rhythm[108] and the likelihood of hypoglycemia in patients based principally on telemetry tracings.[62]

Though powerful proof of concepts, the studies outlined above were largely retrospective in nature. In order to successfully embed ML algorithms into everyday practice, this work must be prospectively validated. Prospective ML-based cardiovascular work is beginning to emerge largely centered around the use of wearable devices.[109] However, despite cardiology's reputation as a data-rich specialty, up until 2019, cardiovascular-related trials encompassed only 11.75% of overall ML-affiliated clinical trial output (Figure 2A, see Supplementary Materials for more information). Furthermore, these studies have taken place in a relatively small number of countries worldwide (Figure 2B, see Supplementary Materials for more information).

There are a number of studies in other clinical domains that effectively demonstrate prospective ML trials. In a recent

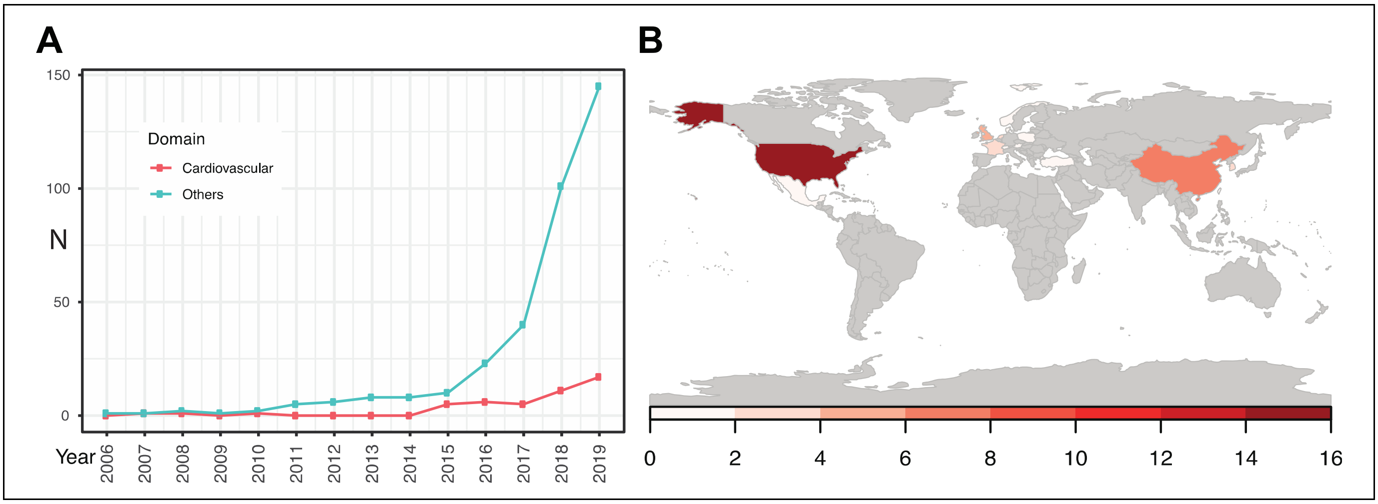


**Figure 2.** A, The trend of ML-affiliated clinical trials per year: cardiovascular-related trials against all other clinical domains. These trials include those who are active, recruiting, enrolling, or completed. In total, 47 (11.75%) of these trials are cardiovascular-related compared to 353 of all others combined. Data were compiled from https://clinicaltrials.gov (see Supplementary Materials or https://github.com/BenGlicksberg/JCPT_Review_2020). B, The number of cardiovascular-related ML clinical trials across the world. The distribution of cardiovascular-related clinical trials that utilize some form of ML by country. These trials most commonly occur within the United States (n = 16), followed by China (n = 8), and then the United Kingdom (n = 5). Data were compiled from https://clinicaltrials.gov (see Supplementary Materials or https://github.com/BenGlicksberg/JCPT_Review_2020). ML indicates machine learning.

study, Wang et al performed a double-blind randomized control study for implementation of a colonoscopy with computer-aided detection (CAD) framework.[110] Here, they prospectively enrolled patients undergoing a screening colonoscopy and provided the treating endoscopists with either the ML-predicted risk estimates or a sham value, that is, a randomly generated number. The primary outcome of this work was adenoma detection rate, and the researchers found the CAD system significantly outperformed the sham group for detection (34% vs 28%). Additionally, McCoy and Das designed and implemented an ML-based sepsis prediction algorithm within a medical center.[111] In their work, they compared the rates of sepsis-related outcomes, specifically inhospital mortality, length of stay, and 30-day readmission rates, between pre- and postimplementation. They found a significant reduction of mortality (60.24%), length of stay (9.55%), and 30-day readmission (50.14%) when using their algorithm compared with preimplementation values.

## Creating Digestible Results and a Culture of Sustainable Innovation

Perhaps one of the most pervasive obstacles to the introduction of ML in mainstream medical practice is the relative lack of transparency when evaluating and publishing results.[112] Though ML techniques are powerful and can be highly accurate, it is often challenging to trace how predictions are obtained. In this way, ML results are not always readily digestible by the general public. Over time, this may cause a lack of trust in both clinicians unfamiliar with ML principles and patients who are attempting to decide between various therapeutic modalities.[113] Recent guidelines place a substantial focus on enhancing clarity for practitioners,[114] and there are a number of efforts currently underway to help make ML models generally more interpretable,[115] including those utilized within the clinical space. In fact, a whole discipline has been developed that is dedicated to the issue of the interpretability of models for implementation.

While the complexity inherent to ML research could represent a substantial barrier for mainstream ML utilization in the clinical setting, some believe that efforts should be less focused on trying to interpret black-box models and instead focus specifically on algorithms that are interpretable by nature.[116] An alternative point of view is that demystifying the black box is not always necessary and that, with rigorous study design, the field should become receptive to results from such algorithms without interpretable explanations.[117]

Either way, an added layer of complexity occurs when considering the doctor–patient relationship. Patients seek the expert opinion of their physician and are frequently offered various treatment options for managing acute or chronic disease. This process becomes extremely challenging when physicians are unable to readily translate the results of ML-based clinical research to the care of their patients. This leads to an inability to fully engage in the shared decision-making process, which can lead to a sense of overwhelming responsibility for the patient and a compromised therapeutic alliance between the physician and the patient. For example, it is already challenging for a patient to decide whether to proceed with prophylactic mastectomy based on her breast cancer susceptibility risk, let alone make that decision without her doctor being able to describe the evidence characterizing her increased risk because its involvement with ML. In cardiology, similar discussions could occur in patients deciding on whether to pursue anticoagulation for their atrial arrhythmia, which cholesterol-lowering medication to take, whether to undergo an invasive stenting procedure based on myocardial infarction risk, or whether to undergo TAVR as opposed to open aortic valve replacement based on an ML-based mortality or periprocedural heart block risk calculator. In this way, lack of familiarity with ML among clinicians is problematic. Essentially, no curricula teaching medical students, residents, or fellows about ML or how to critically evaluate ML-related research papers currently exist.[118,119] It is essential to begin introducing ML concepts within the modern-day medical education curriculum, and carefully designed systems should be developed to appropriately convey output of ML risk models during patient interactions, perhaps through the use of interactive dashboards.[120] These tools should emphasize the need for ML literacy among trainees and clinicians rather than the need for classroom- or program-wide ML expertise. Clinicians should be familiar enough with ML to consider it a useful tool in their arsenal when deciding on the most appropriate screening, diagnostic, and therapeutic modalities for their patients. In sum, creating a culture of comfortability among clinicians and patients regarding ML algorithm results is not only important but vital to the success of making ML more mainstream in health care moving forward.

## Conclusions

Despite immense cardiovascular research breakthroughs over the past few decades, substantial challenges and questions pertaining to cardiac pathophysiology and clinical management remain.[121] Not only is CVD the most prevalent killer in the United States and around the world, it is also multifactorial and highly complex in nature. These challenges have necessitated the development of novel methods for scientific exploration and thorough data analysis. Simultaneously, improvements in computing power and data storage have coincided with more streamlined electronic medical documentation, leading to refined data storage methods. Machine learning represents a uniquely promising avenue to better understand pathophysiology, analyze increasingly large and complex sets of data, and ultimately improve medical screening, diagnosis, and therapeutics for the millions of patients suffering from acute and chronic comorbidities. Despite large institutional ML investment, substantial promise for reduced health-care expenditure, and the potential for a fundamental transformation in the way disease is understood and managed, there has been a noticeable lack of impactful published ML-based clinical research that has been successfully translated into clinical practice. This trend is particularly true in cardiology, despite its status as a data-rich specialty. Reasons for this are multifactorial but include poor project development, lack of complete and uniformly entered data sets, poorly transparent results, and an overall lack of clinician and patient comfortability with ML concepts. The amount of hype associated with ML juxtaposed against the relative dearth of clinical impact poses a serious threat to biomedical ML's growth and reputation. This has a direct impact on ML's utility in medicine. With the advent of new reimbursement models, including pay for performance methods such as the Merit-Based Incentive Payment System and the Hospital Readmissions Reduction Program,[122] health-care institutions are being incentivized to demonstrate improved outcomes or other metrics to justify investment. Perhaps even more importantly, clinicians who have yet to witness clinical impact are unlikely to devote the time and energy necessary to learn ML principles and equip themselves to critically evaluate relevant ML research publications. These obstacles could stifle the field's enormous potential. Without a change in approach, patients who may have benefitted from this technology would not be receiving optimal care, and ML could come to represent a missed opportunity rather than a transformative technology. In this article, we have summarized recent ML-based research efforts in cardiology and have outlined strategies for the successful production and communication of clinically impactful and sustainable results. Machine learning has immense potential and may represent the most fruitful way to understand CVD over the long-term.

### Author Contributions

All authors contributed to the preparation, writing, and editing of this manuscript.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: KWJ has received funding and holds equity in Tempus Labs. GNN is cofounder of and owns equity in Pensieve Health and is a cofounder and member of scientific advisory board of and owns equity and options in RenalytixAI. GNN also reports receiving consulting fees from AstraZeneca, BioVie, Inc, GLG Consulting, and Reata Pharmaceuticals in the past 3 years. SS is a cofounder of and owns equity in Monogram Orthopedics. All other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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### Supplemental Material

Supplemental material for this article is available online.

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