Exclusive preview: AI in Cardiovascular Medicine

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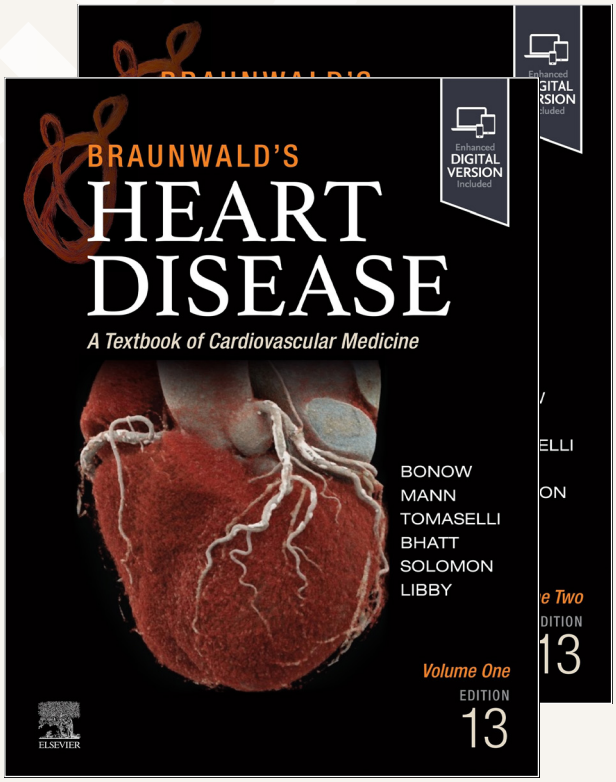

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10 Artificial Intelligence in Cardiovascular Medicine

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KEY POINTS

- Artificial intelligence (AI) is substantially improving the diagnostic capabilities of existing medical tests. This advancement is leading to earlier and more accurate diagnoses of cardiovascular diseases.
- AI is enabling the deep phenotyping of individuals. This detailed analysis stands to assist in tailoring personalized treatment plans, embodying the principles of precision medicine in cardiovascular care.
- AI tools can diagnose cardiovascular conditions on a large scale, relieving the burden on health care systems by detecting occult (hidden) diseases and predicting future disease risks and enabling primary care providers to screen more effectively for cardiovascular disease.
- Although still in early development stages, clinical trials are increasingly demonstrating AI's effectiveness. AI offers the ability to extract clinically relevant information from wearable devices, even in nonmedical settings.
- Clinicians today need to understand the basics of how AI works, its strengths and limitations, and when to trust AI-generated results. This chapter provides foundational information to that end.

Artificial intelligence (AI) is ubiquitous. It autocompletes the sentences we type, populates web searches before we complete our thoughts, enables our phones to understand verbal commands, permits cars to drive themselves to destinations we speak, and increasingly is used in support of medical diagnostic tests. In medicine, it has identified retinal pathology with a skill that exceeds that of a trained ophthalmologist, can tirelessly detect mammographic lesions, and can identify abnormalities on a pathologic slide. It has been vilified as a technology that will lead to massive unemployment and economic disruption, presenting an existential threat to humanity. Alternatively, it has been deified as the tool that will liberate humanity from drudgery and elevate the most noble of human tasks.[1]

AI can be predictive or generative. Predictive identifies patterns within a data stream (electronic medical record [EMR], electrocardiogram [ECG], images) and provides additional inferences. Generative AI creates text and/or images, in response to queries or by extracting and or summarizing preexisting documents, using a vast storehouse of data to inform its responses. Predictive AI has early approved uses in medicine, with many more in the pipeline. Generative AI holds dramatic promise but is in earlier stages of development. This chapter focuses predominantly on predictive AI.

Medicine encompasses three broad capabilities of AI. The first is the automation of fatiguing processes that involve analysis of massive amounts of data, such as continuous ECG tracings acquired over months. In this context, AI performs human-like tasks at massive scale. This also permits embedding technology in novel forms such as clothing and other wearables to extract physiologic information to monitor health continuously. These advances enable remote monitoring in rural locations, space exploration, and extreme conditions. The second is the ability to extract signals beyond those a human is capable of recognizing—for example, determining the presence of ventricular function from a standard 12-lead electrocardiograph or single-lead ECG acquired from a watch- or smartphone-enabled electrodes. In this context, AI brings new value to well-established medical diagnostic tests that exist in current clinical workflows and practice. Third, and more broadly, the ability to characterize specifically, richly, and uniquely an individual's physiologic data allows for a new level of personalized predictive models, potentially creating a whole new category of individual "previvors," who learn of impending disease before any signs or symptoms develop, permitting potential interventions, with associated social, legal, and economic implications. This deep phenotyping may inform additional fields, such as genetics. AI in medicine is in its early stages; the promise is large, but requires rigorous testing, vetting, and validation, as do all tests that affect human health. Here we focus on AI and its role in cardiovascular (CV) medicine.

DEFINITIONS AND KEY TERMS

> If intelligence is a cake, the bulk of the cake is unsupervised learning, the icing on the cake is supervised learning, and the cherry on the cake is reinforcement learning (RL).
>
> *Yann LeCun, 2016*

AI is a lay term, referring to machine learning (ML). In his cake analogy, Dr. Yann LeCun,* divides ML into its three main branches and presents

*Yann LeCun, Geoffrey Hinton, and Yoshua Bengio, often referred to as the Godfathers of AI or the founding fathers of modern AI research, were awarded together the prestigious Turing Award in 2018 for their contribution to the AI revolution.

one of the technology's main challenges: the amount of data required for implementation. In all three types of learning (supervised, unsupervised, and reinforcement), instead of using an explicit set of human-devised rules to interpret a signal, large volumes of data are fed to a model, which uses statistical processes to identify relationships within the data.[2] Recent advancements have led to the creation of generative AI, which uses all of the factors described here to create new, realistic data. This exciting frontier is designed to generate novel data that mirror real-world examples. Generative AI harnesses the capabilities of supervised, unsupervised, and reinforcement learning to synthesize new and realistic data patterns. In short, the data train the model, free from human hypothesis (eFig. 10.1).

Learning

Learning is the enhancement of abilities through experience. As the task is repeated, ML improves by getting feedback (via an error or loss function) and changing the way it performs the task (e.g., by changing with weights and biases the mathematical functions that make up the neurons in a neural network), until feedback indicates that the task is done correctly, or at least above a certain standard. With ML, feedback comes from a loss function, which measures the gap between the expected and actual outcomes. Training is computationally demanding. Once trained, many networks can then operate with limited computational resources, for example, on a smartphone. This makes many AI tools massively scalable.

SUPERVISED LEARNING

Supervised learning is the most commonly used form of ML. Supervised learning requires labeled data (images and captions, ECGs and their rhythm description), with labels often provided by human experts. The discovery of the rules that explain the relationship between the input (a signal) and the output (a label) is called *training*. For example, if ECG samples labeled normal rhythm or atrial fibrillation (AF) are fed to a model, it will learn to differentiate between the two rhythms. The specific features of the signal used to generate model output are determined by the computer during training and are not discernable to humans (Fig. 10.1). Thus, AI is at times referred to as a "black box." In most cases, the model will be a parametric function *(F)* of the inputs, and it will be initialized using a set of random parameters (weights). During training, in an iterative manner, *F* is applied on a set of inputs with known outputs (the labels). The results of applying the function *F* on the inputs yields estimated outputs (in the previous example, the probability of AF. Each iteration assesses model performance through the error between predicted and true labels, tuning the function's weights to minimize this discrepancy. Further weight adjustment details are described in the "Optimization and Hyperparameters" subsection of this chapter. Tasks in supervised learning can be either classification, such as determining categories (e.g., dogs vs. cats), or regression, predicting continuous values such as age from an image. The iterative approach of supervised learning necessitates large, labeled datasets.

UNSUPERVISED LEARNING

In unsupervised learning, the task revolves around the structure of the data itself. The most common form of unsupervised learning is *clustering,* in which the model clusters data based on characteristics, instead of labels, during the training stage. The model is fed only unlabeled data, and clusters samples based on similarity, using each sample's distance (euclidian or other) from other samples. If the label of just a few samples in each cluster is known, the label of other samples in the cluster can be inferred because all the samples in that cluster would have similar features. An example would be the acquisition of multiple ECG segments from a patient at various potassium blood levels (e.g., at various times during dialysis). The ECG segments could be clustered, and the potassium value of each cluster should be similar. Unsupervised learning requires only the raw samples and basic assumptions regarding the data structure (e.g., the number of clusters); therefore, the barrier imposed by labeled data is lowered.

REINFORCEMENT LEARNING AND REINFORCEMENT LEARNING FROM HUMAN FEEDBACK

Reinforcement learning (RL) develops the optimal strategy for an agent in an environment with known rules and rewards. An example would be a chess player learning chess by playing against itself, without labels or recorded human games. It uses only the rules and the game score. Reinforcement learning from human feedback (RLHF)

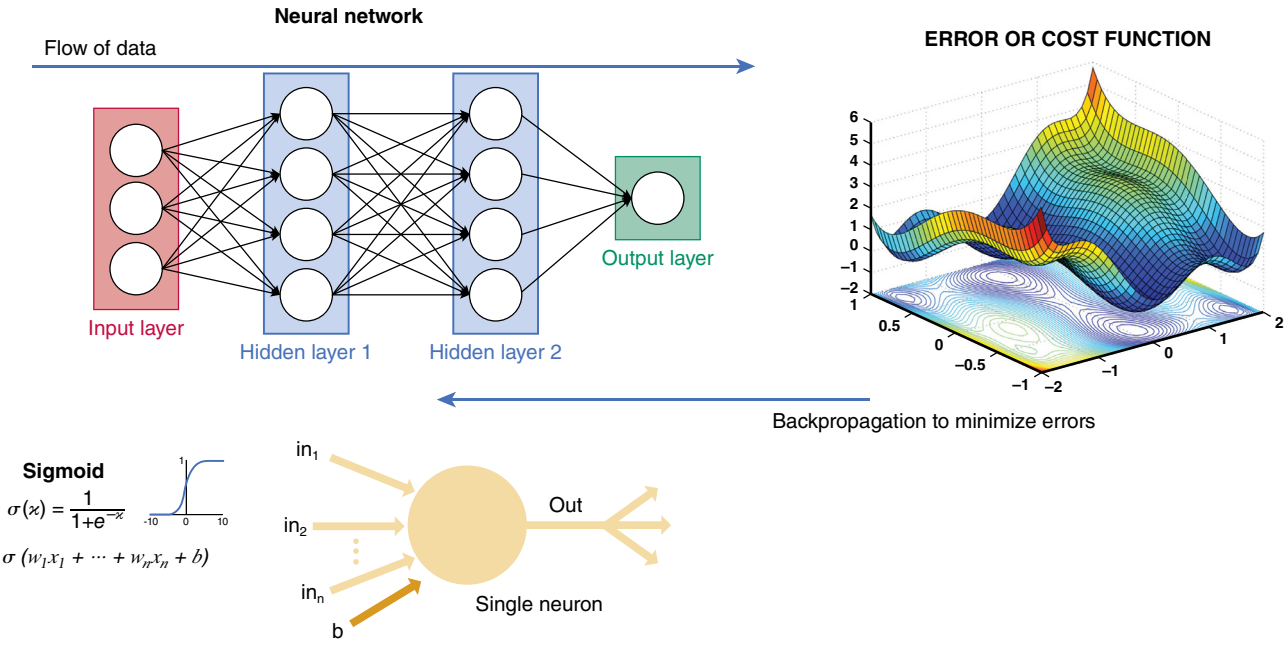


FIG. 10.1 Graphical depiction of a neural network. *Top left,* The neural network shown contains four layers. Each layer is composed of "neurons" *(bottom panel).* Each neuron receives multiple inputs, each multiplied by a weight ($in_1 \ldots in_n$), and a bias (offset) *"b"* and applies a nonlinear function to generate its output. During network training, weights and biases of each neuron are adjusted by back propagation to minimize an error function (example error function shown *top right*).

combines RL techniques with human feedback to optimize AI agents, especially in contexts such as natural language processing. This approach allows for more accurate fine-tuning, especially when subtleties and nuances of tasks, such as chat interactions, are involved.

Traditional RL requires known rules and rewards; thus, its direct use in health care can be limited. RLHF offers a more nuanced approach by incorporating human feedback, but a comprehensive exploration of its use in health care is outside the scope of this chapter.

Fully Connected and Convolutional Neural Networks

Inspired by the human brain, a fully connected neural network is a multilayer parametric function that implements a nonlinear function between the inputs to the outputs (see Fig. 10.1) Each node (neuron) in each layer receives a weighted sum of all the nodes in the preceding layers and is activated using a nonlinear function. The values of the weights are defined during training, as the network learns the relationship between the input and output.

In convolutional neural networks, convolutional filters extract feature information from images in the initial layers, with the weights of the filters determined during training, so that the features selected are those that best define the desired network output. Both types of networks can be either used for classification tasks or for regression tasks.

Optimization and Hyperparameters

During training, the weights of the inputs to each neuron in a neural network adjust to bring the outputs closer to their real labels. The difference between network output and the actual label is measured using a loss function, with smaller loss values indicating closer outputs. Instead of randomly adjusting weights, a more efficient method is to assess the effect of each weight on the error and adjust accordingly. This involves calculating the gradient of the function and adjusting weights in the opposite direction. The gradient is approximated using a batch of samples, and the number of samples in the batch (batch size) influences its accuracy. The gradient provides direction for adjustment, but the magnitude, or step size, remains uncertain. If too large, the adjustment can overshoot optimal performance, and, if too small, progress may be too slow. Step size and batch size are hyperparameters, affecting the training but not part of the final function. Determining optimal hyperparameters often involves trial and error and is tested on an internal validation set. Once finalized, the network is evaluated on a holdout testing set.

Transfer Learning

Transfer learning is method used to apply supervised learning to problems for which the data sets available to train a network are relatively small. In this method, a network is developed to solve a problem that has enough labeled samples (the primer) and then is retrained to solve a similar task with a much smaller dataset. The underlying hypothesis is that some of the patterns learned by the model are common to both tasks, but can only be learned with a sufficient number of samples. This is similar to a human learning one musical instrument proficiently over years, and then requiring much less time and effort to learn a related instrument (e.g., guitar and banjo). Using transfer learning, datasets that may initially appear irrelevant can be employed to solve specific tasks, and the transfer can be applied to all model parameters (basically seeding the model with weights from a trained model, instead of random weights), or to only a subset of parameters by freezing some model layers during training to keep the primer model values, but allowing the rest to change.

FOUNDATIONAL MODELS

Building on the principles of transfer learning, in which models initially trained for one domain are repurposed for another, the advent of foundational models represents a significant leap in AI. These robust models, enriched by their training on vast datasets, do not just harness the concept of transfer learning but elevate it. They serve as a potent base (and are often called base models), drawing on shared commonalities across various tasks, ready to be specialized and adapted. Foundational models, distinguished by their immense scale, can encapsulate billions of parameters. This enormity enables them to recognize and represent intricate patterns within data, often beyond the discernment of simpler models. Their initial training equips them with a versatility reminiscent of the underlying ethos of transfer learning. Just as transfer learning underscores the shared features across different tasks, foundational models, with their expansive pretraining, emerge as versatile juggernauts capable of pivoting across diverse domains.

Generative Artificial Intelligence

Generative AI distinguishes itself from other AI forms by its ability to produce new data instances that are not part of its initial training data. This contrasts with discriminative models, which focus on distinguishing between given categories or predicting continuous values in regression tasks. Whereas discriminative models, like those used in standard classification or regression tasks, delineate boundaries between classes or predict outcomes based on input features, generative models aim to understand the underlying distribution from which the data originate. This inherent distinction allows generative AI to create images, sounds, and even text that mirrors genuine data, unlocking vast possibilities, especially in the medical arena.

Operating primarily within the unsupervised learning paradigm, generative AI does not rely solely on labeled data. Instead, it learns the underlying patterns and distributions inherent in the input data. Techniques such as generative adversarial networks (GANs) and variational autoencoders (VAEs) exemplify this approach. However, there is a fascinating overlap in which generative models can benefit from other learning techniques. Semisupervised learning, for instance, leverages generative models to augment datasets with labeled data, enhancing the performance of tasks with limited labeled samples.

In recent advancements, products such as OpenAI's ChatGPT and their underlying models (GPT 3.5/GPT 4) have shown the extensive capabilities of generative AI. These models, especially the newer iterations, are not just trained on vast textual datasets using unsupervised and supervised learning; they also incorporate RLHF to refine their responses. Such techniques enable more accurate, contextually aware text generation, proving invaluable in medicine for patient interactions, literature summarization, and diagnostic assistance. On the visual spectrum, GANs and diffusion models, such as DALL·E, can generate images based on textual cues, paving the way for potential applications such as medical imagery generation or data augmentation. Additionally, generative models capable of predicting molecular structures have enhanced drug discovery, optimizing the journey from laboratory to patient. It is imperative to acknowledge that although these models offer vast potential in health care, their use in critical sectors requires meticulous validation, considering the import of medical decisions.

The integration of generative AI into medicine promises a pioneering era, foreseeing rapid research advancements and a heightened quality of patient care. Progress in this arena could transform health care.

CLINICAL USES IN CARDIOVASCULAR MEDICINE

Electrocardiography-Based Screening, Detection, and Prevention

Achieving human-like automated ECG interpretation has been a goal since the advent of digital ECG recording more than 60 years ago.[3] Early iterations of the technology were designed to identify fiducial points, make discrete measurements, and define common quantifiable abnormalities,[4–6] whereas contemporary approaches have moved beyond these rule-based approaches to recognize patterns in massive quantities of labeled ECG data.[7–9] Some early success has been achieved training deep neural networks on large datasets of single-lead ECGs and applying the algorithms to the 12-lead ECG,[8] sometimes outperforming expert over-readers.[7]

For some discrete applications, these algorithms may enable rapid diagnosis on novel, patient- or consumer-facing devices. For example, algorithms can effectively diagnose AF using a variety of single-lead ECG devices,[10–13] and offers great potential for making other important diagnoses, including QT prolongation,[14] acute myocardial infarction,[15] or other arrhythmias[16] (Video 10.1). This "democratization" of ECG technology will exponentially increase the volume of signals that demand interpretation, and this will quickly outstrip the capacity of human ECG readers. We anticipate that these models will facilitate telehealth technologies and automatic, patient- or consumer-facing technologies.

By leveraging massive, labeled datasets, various neural networks can move beyond human-like tasks to uncover more subtle patterns in the ECG previously unrecognized even by expert ECG readers. Thus, these networks can bring new diagnostic power and value to the ECG. For instance, the ECG can identify low ejection fraction (EF),[17] propensity toward AF (observable during normal sinus rhythm),[18] hypertrophic cardiomyopathy (HCM),[19] left ventricular (LV) hypertrophy,[20] hyperkalemia,[21] age and sex,[22] medical comorbidity/frailty, valvular heart disease,[23,24] amyloidosis, coronary artery disease,[25] and many other conditions.

Artificial intelligence–electrocardiography (AI-ECG) is an example of adding AI to an existing clinical test (the 12-lead ECG), which is already embedded in clinical workflows and widely available. Thus, it can readily screen for underdetected disease, for which therapies exist (Fig. 10.2A). The use of the 12-lead ECG to identify LV dysfunction (present asymptomatically in 3% to 9% of people) has been prospectively evaluated in a large cluster-design pragmatic trial (EAGLE, discussed later); the AI-ECG has also been embedded into a stethoscope device to effectively screen for ventricular dysfunction in the British National Health Service (NHS).[26] Because of the potential sensitivity of AI tests to detect disease early and provide deep phenotyping, it may appear to "predict" future disease, creating a class of "previvors" who have not yet experienced a disease (see Fig. 10.2B). The AI-ECG may also permit inexpensive at-home observation of patients at risk for ventricular dysfunction, such as those receiving chemotherapy or cardiac transplants (see Fig. 10.2C). Prospective studies assessing such use cases are under way (TACTIC, NCT03879629). Whether AI tests achieve a sufficient level of predictive power to warrant intervention before a disease manifests by currently used tests requires validation (Fig. 10.3), which at present is under development. US Food and Drug Administration (FDA) approvals for novel uses of established tools such as the ECG with the additional AI continue to accumulate (further discussion later).

Clinical Trials of Artificial Intelligence Electrocardiography

With an increasing number of AI and ML algorithms for early disease detection, attention has increased on how to evaluate them best in the clinical arena. As with any new clinical technology, it is critical to evaluate algorithms systematically to understand better the clinical cost and relative impact they may have in patient care. Prospective clinical trials to assess (1) accuracy, (2) safety, (3) reliability, and (4) cost. In the realm of AI applications to the use of ECG to allow for early prediction of a variety of disease states, multiple recent clinical trials have supported the potential impact of these algorithms.

ARTIFICIAL INTELLIGENCE–ENABLED EARLY PREDICTION OF LOW EJECTION FRACTION

In the prospective ECG AI-guided screening for low ejection fraction (EAGLE) study, Yao and colleagues[27] demonstrated the utility of an AI algorithm employing the 12-lead ECG for the early prediction of low EF within a primary care practice. The study design demonstrated rapid enrollment of software-based interventions (over 23,000 patients in 8 months) with a modest budget. This innovation significantly improved the diagnosis of low EF when compared to routine clinical practice.[28] Across 120 primary care teams distributed across 45 clinics and hospitals, the control group exhibited a low EF diagnosis rate of 1.6%, whereas the intervention group, which employed the AI algorithm, reported a 2.1% diagnosis rate, with similar echocardiography use. These results underscore the effectiveness of AI-based algorithms using ECGs in enabling the early diagnosis of low EF within primary care settings. The AI-ECG has received FDA approval for screening for LV dysfunction.

Beyond primary care, other studies have explored the application of AI algorithms for low EF detection in clinical and ambulatory settings using advanced ECG monitoring devices, such as stethoscopes with integrated ECG electrodes for ECG acquisition during physical examinations and wearable smartwatches that allow patients to record their own ECGs.[29,30] A study involving 100 patients undergoing echocardiography revealed that the AI algorithm applied to ECGs recorded from an ECG-enabled stethoscope reliably detected low EF, with an area under the curve (AUC) of 0.91 for EF less than 35%, 0.89 for EF less than 40%, and 0.84 for EF less than 50%. Similar results were found using the stethoscope in 1050 primary care patients seen in the UK NHS.[26]

A prospective evaluation applying the AI algorithm to single-lead ECGs acquired from a smartwatch demonstrated the impact on clinical trials. Patients who had been seen at Mayo Clinic were remotely enrolled, resulting in inclusion of 2454 unique patients from 46 US states and 11 countries in 5 months, who transmitted over 125,000 ECGs acquired in nonmedical environments. The watch ECG had an AUC of 0.89 for identifying patients with an EF less than 40%. These trials affirm that AI-based algorithms for predicting low EF can be extended to nontraditional ECG sources, acquire signals in nonmedical environments, be assessed using inexpensive, novel study designs, and accurately identify patients with undiagnosed cardiomyopathy, even in the absence of symptoms.

ARTIFICIAL INTELLIGENCE–ENABLED EARLY IDENTIFICATION OF ATRIAL FIBRILLATION

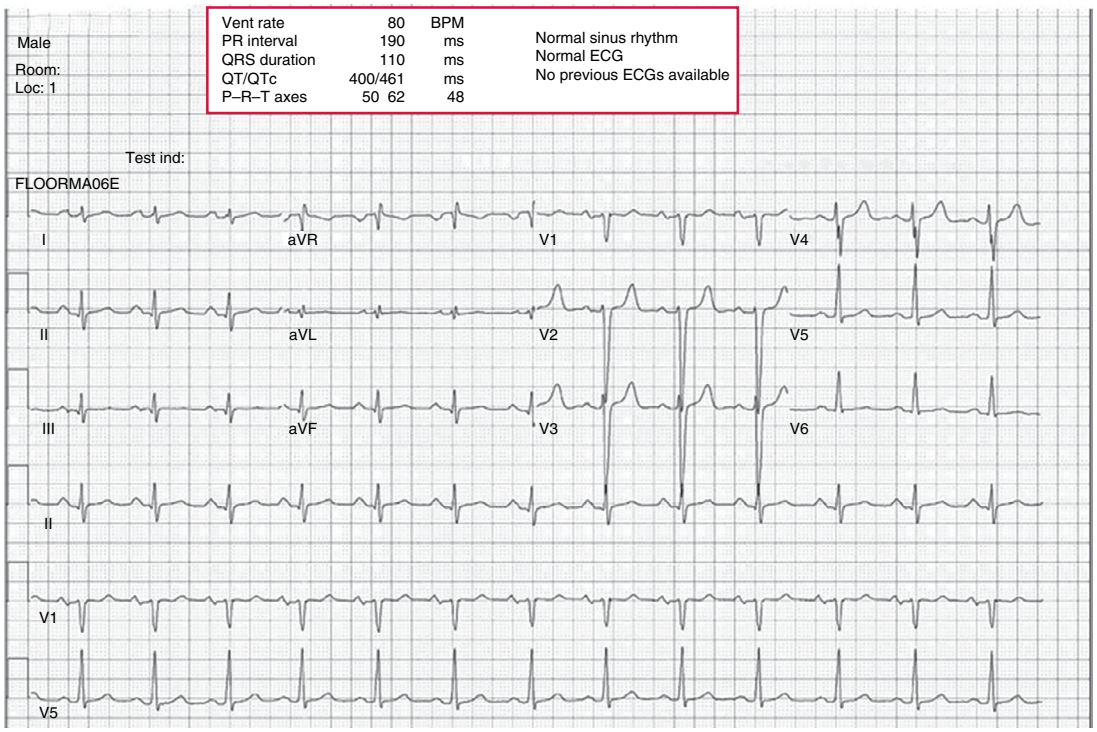
Among patients with undiagnosed AF, early identification, particularly for those at increased stroke risk, is critical. The BEAGLE study processed stored sinus rhythm ECGs from patients previously seen at Mayo Clinic with no known history of AF to screen for AI-detected silent AF. Patients were then contacted and offered a 30-day monitor if they had a high CHADSVASC score. Among 1003 patients recruited from across the United States, those with a high-risk AI-ECG for silent AF were more likely to experience AF during monitoring than those with a low risk (odds ratio approximately 5) or than those undergoing usual care.[31] These data indicate that an AI-guided targeted screening approach can significantly increase the yield of AF detection and thus improve effectiveness of screening.

ARTIFICIAL INTELLIGENCE–ENABLED EARLY DETECTION OF HYPERTROPHIC CARDIOMYOPATHY

The PIONEER-OLE trial studied the efficacy of mavacamten in patients with HCM (see Chapter 62).[32] As extension of this trial, an AI algorithm was applied to ECGs from all patients enrolled (N = 13) who were matched against control patients (N = 2600) in a 1:200 ratio. The AI-ECG algorithm to detect HCM was then applied to all ECGs for patients treated in the trial to assess association with the hypertrophic state. To discriminate patients with HCM from those without at baseline, the algorithm yielded an AUC of 0.94, comparable to previous retrospective data underscoring the ability of the AI-ECG to identify patients with HCM, and to distinguish them from patients with hypertensive heart disease. Interestingly, among treated patients, the HCM score provided by the AI-ECG algorithm (higher score = higher likelihood of having HCM) decreased over the course of treatment (mean reduction >40%). These mirrored clinical changes in terms of reduction of LV outflow tract gradient and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. This study not only highlighted the accuracy of the AI-ECG algorithm but also demonstrated that it could assist monitoring over time the disease state of patients with HCM.

ARTIFICIAL INTELLIGENCE DISEASE DETECTION IN SPECIAL POPULATIONS

With the increasing application of AI-ECG screening in the general population, increasing focus has also been paid to applications in special populations. For example, pregnant females or patients undergoing chemotherapy may have an increased risk for developing cardiomyopathy. However, routine echocardiography is time and labor intensive and often not performed. Moreover, many of the symptoms of pregnancy—edema, dyspnea, exercise intolerance—may mimic those of cardiomyopathy. Thus, early screening with inexpensive, safe, and

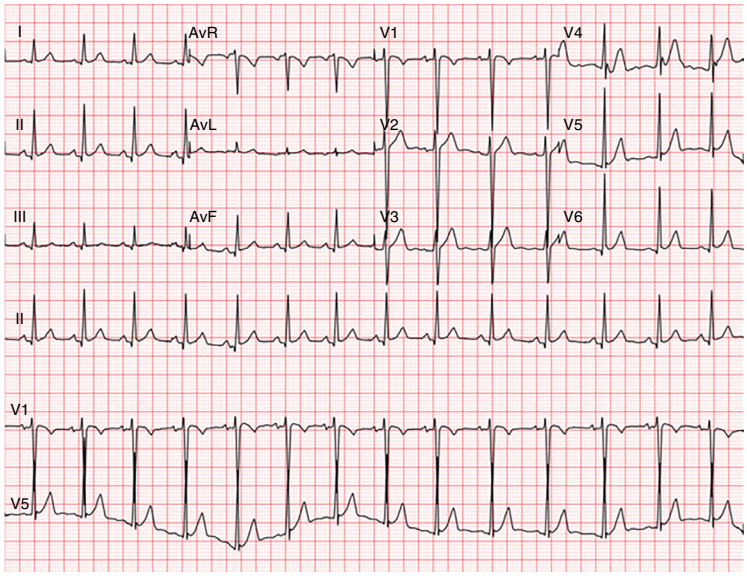


AI-ECG OUTPUT: Positive for low EF (76% probability of having low EF)

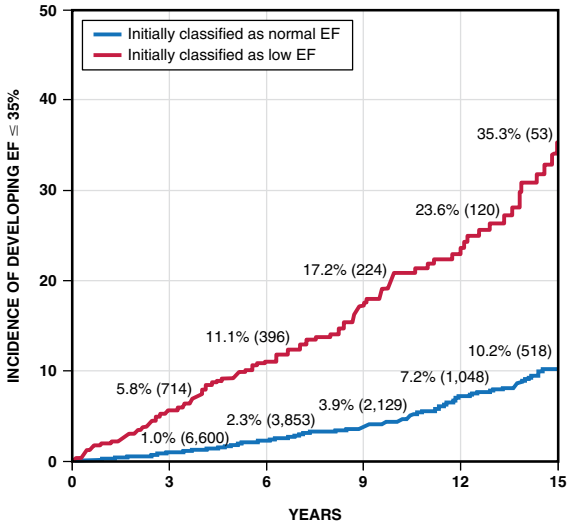
Echocardiogram EF: 18%

A

Normal sinus rhythm normal ECG



AI ECG: Positive for Low EF Echocardiographic Ejection Fraction: 50%: *False-Positive*
Ejection Fraction 5 years later at age 33: 31%



B

FIG. 10.2 (A) Electrocardiogram acquired from a 35-year-old asymptomatic male who presented after his sister died suddenly, read as normal. An AI-ECG algorithm reported a 76% probability of having a low EF. Subsequent echocardiography demonstrated an EF of 18%. He was ultimately diagnosed with familial dilated cardiomyopathy. (B) *Left,* ECG from a 28-year-old male, read as normal. The AI-ECG algorithm indicated a high probability of an EF less than 35% (positive test). Echocardiography at that time reported an EF of 50%, suggesting a false positive. However, the patient developed ventricular dysfunction, with an EF of 31% 5 years later. In some patients, the AI algorithm may be identifying subtle features that may predict future development of low EF. This raises the concept of disease "previvors," and in this case may result from pathophysiologic changes affecting ion channels and electrical impulse generation before mechanical function is affected, although the mechanism remains unproven. *Right,* The increased risk for developing left ventricular dysfunction with a positive AI-ECG screen for ventricular dysfunction.

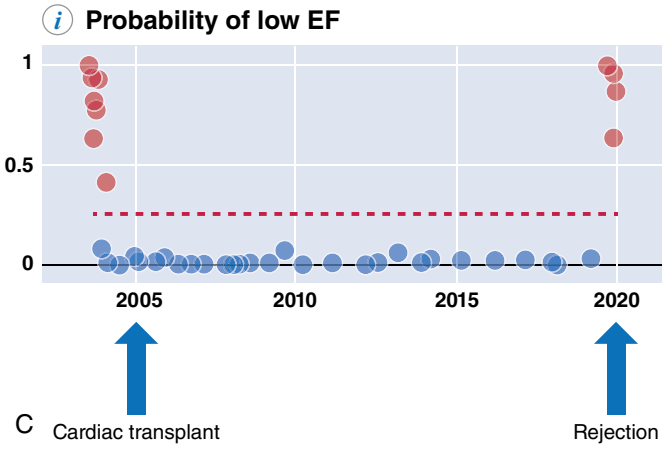


FIG. 10.2, cont'd (C) Plot of the AI-ECG outputs for all of the ECGs for an individual patient, taken from the Mayo Clinic Cardiology AI-Dashboard. Each point on the graph is generated by a single ECG, with the abscissa indicative of the date of the ECG, and the ordinate the probability of ventricular dysfunction. The patient had dilated cardiomyopathy, and confirmed low EF (*red points, left of 2005 on the graph*). He received a cardiac transplant, with normalization of his EF, and subsequent low probability of low EF by AI-ECG (*blue points*). In 2020 he experienced rejection and ventricular dysfunction, identified by the AI-ECG (*red points at 2020*). AI-ECG, Artificial intelligence–electrocardiography; BPM, beats per minute; EF, ejection fraction. (B, right, from Attia ZI, Kapa S, Lopez-Jimenez F, et al. Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram. Nat Med. 2019;25:70–74.)

rapid tests, such as the AI-ECG, may offer particular value in these populations. Clinical trials of pregnant females and of patients undergoing chemotherapy have demonstrated that the AI-ECG algorithm used to detect low EF was highly accurate (similar to findings in the general population) in identifying those with a low EF and better than traditional approaches such as using natriuretic peptide levels or a multivariable model consisting of demographic and clinical parameters (AUC 0.92 for EF ≤35%, 0.89 for EF <45%, 0.87 for EF <50%).[33]

In summary, clinical trials provide a rubric for how to assess AI algorithms in terms of their utility in clinical practice. Additionally, they have demonstrated how pragmatic trials of software as a medical device (SaMD, further discussion later) enable rapid and inexpensive assessment of AI-ECG tools. In aggregate, the AI-ECG algorithms demonstrate a robust ability to maintain accuracy even when applied to nontraditional ECG platforms (e.g., single-lead ECGs obtained via a smartwatch or ECG-enabled stethoscope), as well as across different populations in diverse geographies. Moreover, they can enable faster and more precise diagnosis of disease among patients when applied in routine practice, potentially influencing clinical practice change.

Image Interpretation, Point of Care Ultrasound, and Procedural Guidance

The complex field of cardiac imaging has been a particular focus of modern AI and ML work, in which ML has been used to improve image acquisition, image quality, accuracy of interpretation, and enhancing insights into cardiac physiology.

POINT OF CARE ULTRASOUND

Use of point-of-care ultrasound (POCUS) has increased bedside assessment because of its ease of use and portability. However, although the technology has become readily available to many clinicians (both cardiologists and noncardiologists), image interpretation (e.g., to identify ventricular dysfunction, major conditions such as a pericardial effusion, regional wall motion abnormalities in the setting of myocardial infarction) requires substantial training and expertise. AI has shown value in the accurate and rapid interpretation of images obtained at the bedside. Compared with expert ultrasound readers, AI-assisted LV function assessments or determination of inferior vena cava compressibility were repeatable and comparable to formal transthoracic echocardiographic measurements.[34,35] In addition, the use of AI in POCUS can guide user image acquisition by providing feedback and visual instruction as to how to position and move the ultrasound probe. This results in greater reproducibility in image acquisition among novice users.[36]

NUCLEAR CARDIOLOGY AND STRESS TESTING

Both ECG stress testing and noninvasive nuclear imaging are limited by potential false-positives or false-negatives. The prognostic value of both ECG stress testing and nuclear imaging depends on the patient-specific pretest likelihood of disease and electrocardiographic, clinical, perfusion, and functional variables. One study of over 2000 patients suggested that AI models may surpass the diagnostic accuracy of standard quantitative analysis and clinical visual reading for myocardial perfusion imaging (AUC of 0.83 with an AI model vs. 0.71 with expert reader diagnosis of obstructive coronary disease).[37] Furthermore, deep learning approaches offer statistically significant improvements in per-vessel and per-patient detection of obstructive coronary disease.[1,38]

ECHOCARDIOGRAPHY

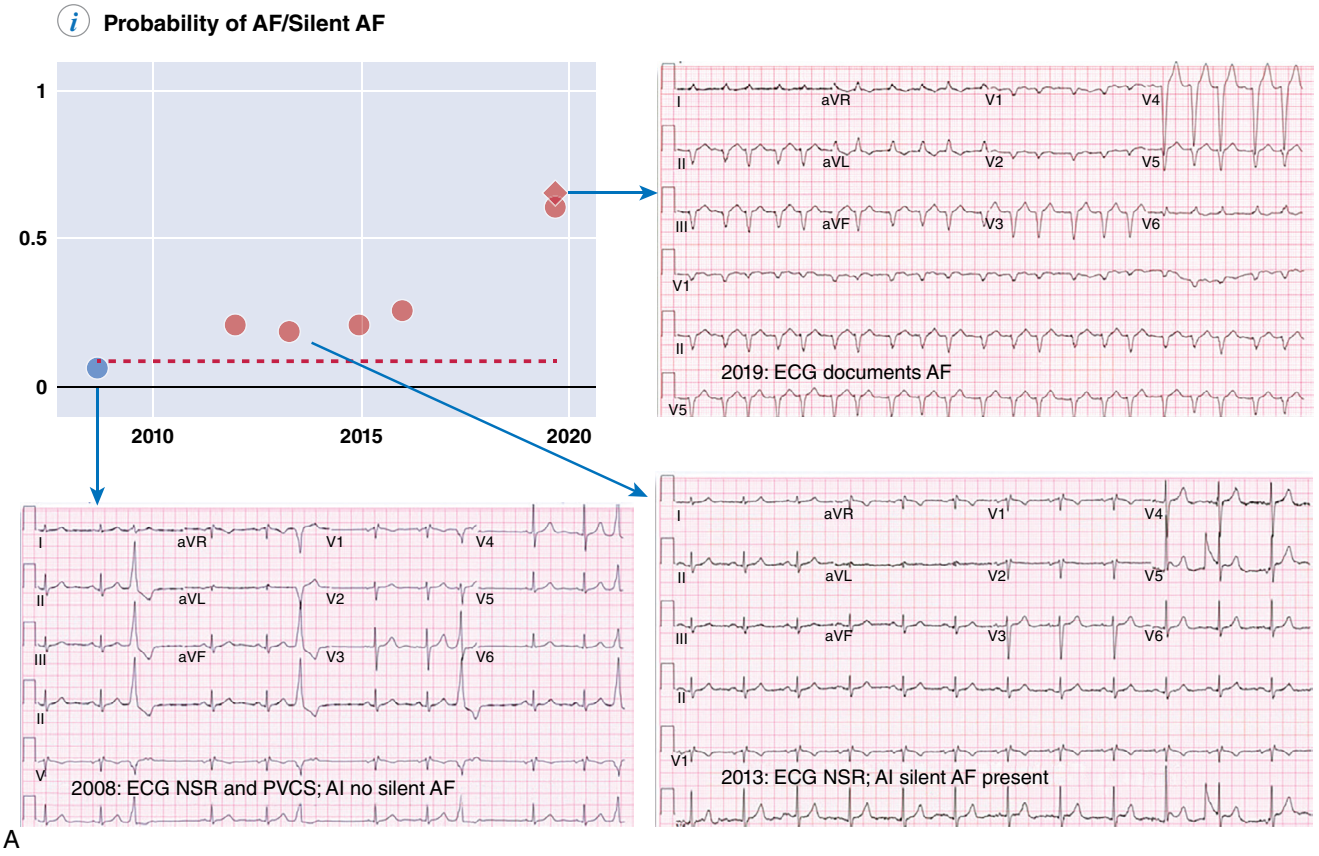
Several factors affect the clinical utility of echocardiographic images: (1) skill related to image acquisition, (2) image quality, and (3) accuracy and consistency of image interpretation.[39] Much work has focused on using AI approaches to facilitate remote training of unskilled sonographers and for robot-assisted echocardiography, with results in improving image acquisition similar to those seen with POCUS. Applying AI to facilitate image acquisition significantly improves diagnostic process time when done in combination with telemedicine-enabled cardiac consultation. AI embedded in the imaging tool recognizes images of diagnostic quality; thus, it offers immediate feedback to the bedside imager (e.g., indicating an image is acceptable, or, if not, suggesting specific maneuvers to acquire the desired image).

In addition to facilitating high-quality image acquisition, the scalability of echocardiographic imaging suffers from the same limitations as other imaging modalities—that is, the need for expert interpretation. Several recent studies have suggested applying ML to echocardiographic images can accurately ascertain several key variables (EF, chamber volumes, valve characterization). One recent global study supported that AI-based analysis of EF minimized variability and increased the statistical power to predict mortality when compared with manual, expert analysis. Thus, such approaches, when applied broadly, may permit rapid and accurate identification of disease and identification of images warranting expert over-read.[40]

In addition, AI approaches have the potential to address other aspects of ultrasound image acquisition, including image noise, poor image quality, and enhancing risk prediction. In various areas of ultrasound imaging, use of ML improves image classification, detection, and segmentation. Methodologic tasks ranging from optimizing imaging quality through the segmentation and registration of such images may be streamlined using integrated AI algorithms.[41]

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Similar to echocardiography and nuclear stress imaging, the expertise of the clinician interpreting the images presents a key limitation of computed tomography (CT) and magnetic resonance imaging (MRI). Several studies have suggested that AI approaches applied to cardiac imaging can improve the consistency and accuracy of interpretation of images. Beyond interpretation, AI approaches to image acquisition may reduce the time required to obtain high-quality MRI and CT



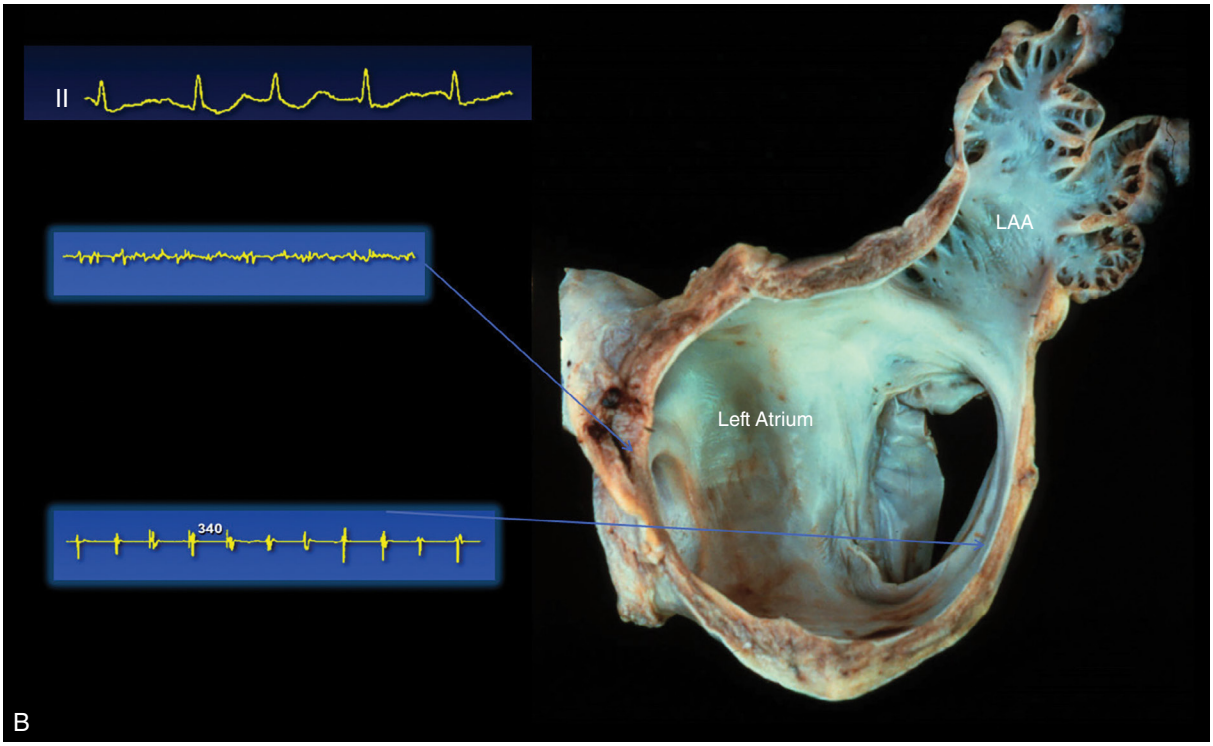


FIG. 10.3 (A) Example of serial electrocardiograms *(ECGs)* from a patient with no atrial fibrillation *(AF)* until 2019. Each dot on the plot on the top left represents an ECG, and three representative ECGs from the plot are shown. AI analysis of the first ECG shown from 2008 does not indicate silent AF. The ECG from 2013 was acquired during normal sinus rhythm *(NSR)*, but AI indicates the presence of silent AF (AF present at other times), as did other ECGs afterward (shown as red dots on the plot). In 2019 AF was finally documented clinically, as shown in the ECG. (B) Surface ECG lead II *(top left),* intracardiac electrogram *(EGM)* acquired from interatrial septum (*left, middle* recording), and EGM acquired from the coronary sinus (*left, bottom* tracing). Note the continuous fractionated signals recorded at the septum, suggestive of fibrosis, as opposed to the discrete signals, separated by isoelectric intervals recorded simultaneously at the coronary sinus during AF. The structural changes, and/or transient repolarization changes before or after AF episodes may lead to subtle changes on the ECG that are used by artificial intelligence–electrocardiography (AI-ECG) to determine episodic AF is present, although the mechanisms by which AI determines the presence of AF from an ECG recorded during NSR is not known. *LAA,* Left atrial appendage; *PVCS,* premature ventricular contractions.

images while reducing motion or other artifacts. Further, AI can scale and improve the speed of segmentation and reconstruction of data from MRI and CT, as well as be useful for risk prediction, showing close association with prognosis and mortality risk. Moreover, recent studies have suggested that AI can be used to facilitate contrast-less myocardial scar assessment, with the ability to virtually allow for scar quantification and spatial assessment equivalent to contrast-enhanced–based approaches. Recent reviews have summarized these benefits.[42,43]

Artificial Intelligence in Invasive Electrophysiology

Application of AI to the electrophysiology (EP) laboratory has increased. The areas of application range from preoperative integration of data into the procedural arena (including integration of CT, MRI, echocardiography, and noninvasive multielectrode ECG scar assessment data) through real-time applications in the EP laboratory. Much current research is focused pre-procedurally on how best to tailor therapy to specific disease phenotypes. For example, in persistent AF, AI tools may help leverage specific clinical and imaging variables to optimize decision-making regarding the appropriate approach (e.g., pulmonary vein isolation, posterior wall isolation). The utility of deep learning specifically may also simplify and make more reproducible approaches to computational heart modeling in the EP laboratory. This application includes aspects of real-time lesion assessment, identifying targets for ablation, and facilitating understanding of endpoints. Further, the use of AI may facilitate outcome prediction or allow tailoring of energy delivery with newer energy sources based on the region targeted for ablation (e.g., in thicker ventricular myocardium vs. thinner atrial myocardium with pulsed field energy).[44,45] The rich data sets and complexity of EP procedures promise substantial value from AI tools, but development is in an early stage and outcome trials are lacking.

Beyond the EP laboratory, evolving work is applying AI to understanding ion channel function and basic EP. This aspect is useful particularly in genetic channelopathy, in which phenotypic expression can be unpredictable with a given gene mutation and with uncertain structure-function relationships. Optimizing pathogenicity prediction may facilitate identification of drug targets or tailoring drug therapy to specific disease types.[44]

Invasive Cardiac Angiography and Hemodynamics

In the field of catheterization, beyond the pre-procedural characterization, AI may help during the procedure to improve consistency of interpretation of images acquired in real time to enhance interpretation of complex lesions. Thereby, ML and deep learning algorithms may facilitate the appropriate choices in management. Recent studies have suggested that, using ML approaches, fractional flow reserve and lesion severity may be extracted from CT coronary angiography and facilitate in-procedure decision-making regarding stent delivery.[46] Aspects such as predicting stent size and length, likelihood of future stenosis, and complex lesion characteristics (irregular lumen shape, invasive fractional flow reserve from cinegraphic images), which would traditionally require the use of additional tools (pressure wires, intravascular ultrasound), represent areas in which AI may offer value in interventional cardiology.[46,47] Further, increasing attention is being paid to the role of AI in facilitating structural interventions such as transcatheter valve repair. AI approaches may aid decision-making on optimal placement of devices in patients to minimize risk and optimize outcomes.[48]

Hemodynamic assessment presents another area for use of AI. Traditionally, hemodynamic evaluation entails invasive right heart catheterization. Furthermore, interpretation of recordings requires expert review to reach an accurate diagnosis. AI may help in the diagnosis of complex hemodynamic issues. Additionally, AI can assess hemodynamics via noninvasive tools such as ECG, auscultation, and other multimodal sensors. Such approaches may facilitate real-time, noninvasive assessment of hemodynamics.[49]

Natural Language Processing, Structured Data Analysis, and Clinical Decision Support

Structured data elements readily available within the EMR enable predictive analytics that can facilitate rapid, point-of-care decision support. However, much of the EMR contains free text that requires additional processing for data abstraction. Traditional rule-based approaches to extract clinical data from free text are prone to misclassification because of the complexities of natural language structure, and more sophisticated models are emerging as more reliable alternatives. These approaches may include hybrid training of models using text vectorization and output tags (representation of text mathematically) that are fed into ML models or even completely unsupervised topic modeling. Further, with the advent of generative AI approaches, a system could read and "learn" from free text charts and provide free text responses based on the contained data. The ability of generative AI to recognize complex language patterns by comprehensively assessing all available documentation may permit improved accuracy in capturing potentially ambiguous diagnoses or to understand better care patterns and thereby build clinical decision support systems aligned with a specific patient's condition.[50]

Risk Scores (Deep Phenotyping)

Structured and unstructured patient data within EMRs offer an opportunity to generate risk scores and characterize patients on a large scale. Deep phenotyping approaches employ a hybrid deep learning model structure to distill the relationships hidden in the data. This may include models that transform event structures into deep clinical concept embedding and use recurrent neural networks to predict outcomes over time. Alternatively, leveraging generative AI may allow for integration of multimodal data to get to more patient-specific assessment of risk. In the Atherosclerosis Risk in Communities (ARIC) study, for example, an ML model outperformed all available regression models, establishing improved risk scores for patients.[51] In addition, one large-scale retrospective study using over three million patient records demonstrated that both traditional statistical approaches and novel ML models can predict risk of AF.[52] Similar approaches can identify patients with heart failure (HF), predict risk of hospitalization, diagnose diabetes and peripheral artery disease, and generally demonstrate performance superior to that relying on structured data alone.[53–55] Both supervised and unsupervised learning approaches and creating repositories of such algorithms have garnered increased attention. For example, public repositories of algorithms, such as the Phenotype KnowledgeBase (PheKB), contain rule-based algorithms for medical conditions, and many have demonstrated good performance when implemented across different health systems.[56] More recently attention has focused on more scalable approaches for algorithm development and application using unsupervised learning approaches, such as via Phe2vec.[57]

IMPLEMENTING ARTIFICIAL INTELLIGENT INTO CLINICAL PRACTICE

AI stands to increase the power of existing clinical tests and transform many mundane accessories (e.g., stethoscopes, shirts, watches) into sources of medically diagnostic information (eFig. 10.2). Edge computing refers to processing signals at the site of data acquisition, limiting transmission time and cost, whereas central processing provides greater computation power. Hybrid approaches using sensors, smartphones, and central processing are emerging as well.

Several key issues need to be addressed as computational algorithms are applied to clinical cardiology practice. Clinical standards will need to ensure optimal and responsible approaches to testing and validation of these algorithms. Concerns remain related to algorithmic bias, such as diversity of the training datasets, selection of an appropriate and specific training target (asking the right questions when training algorithms), how to best ensure that an algorithm will function similarly on data acquired at a location different from where the initial algorithm was developed (reproducibility), transparency, and model explainability. Furthermore, studies are needed to understand how best

to optimize real-time, clinical implementation of AI-enabled alerts. For example, AI algorithms that streamline data acquisition, interpretation, and reporting may integrate more easily into practice. However, as such algorithms become more embedded into health systems, the potential for human oversight and correction may decrease. In turn, AI-managed alerts that permit recognition of disease (e.g., detection of LV EF from a 12-lead ECG) may not have substantial impact if not implemented in such a way that physicians can react appropriately to the alert. A few clinical trials have evaluated the clinical impact of AI algorithms, as noted earlier. AI-guided screening proved superior to usual care in identifying unrecognized AF.[31] A blinded, randomized trial comparing sonographer initial assessment of LV function to automated AI initial assessment showed an AI-guided workflow was noninferior and superior to sonographer assessment and was associated with improved efficiency in the clinical interpretation of echocardiograms.[58]

Mayo Clinic has developed an AI Dashboard accessible via the EMR that automatically ingests all clinical ECGs available in the EMR and patient-recorded smartwatch ECGs transmitted to the EMR using a Mayo Clinic ECG app. The dashboard displays multiple AI analyses in an interactive, graphical format (Video 10.2; eFig. 10.3) to facilitate the incorporation of AI-based results into an existing clinical process to facilitate and improve patient care.[30,59]

Other key areas of consideration when implementing AI and ML into clinical practice include how to allow continuous adaptation of the algorithms to new data, associated regulatory implications, and how algorithms and data should interact. Continuous exposure to new data, which improves diversity of cases to which a clinician gets exposed, improves clinical expertise. Similarly, systems that use AI algorithms will continue to evolve in response to their correct and incorrect interpretations, strengthening the overall model over time. However, regulatory standards and approval of adaptive algorithms may vary among countries.[60] The question of how algorithms are practically and effectively deployed across institutions or countries remains to be determined. Many algorithms require large computational resources (high energy and memory requirements) and can only operate in cloud-based systems. However, many data frameworks impose restrictions on sending data to centralized cloud-based servers. Supplying algorithms to individual institutions limits the opportunity for continuous learning and leads to potential scalability issues because of the availability of adequate computational power at every local site. In addition, the use of cloud-based systems that allow data to be sent to a centralized framework creates concerns regarding data sharing and data privacy. Edge computing, blockchain, and federated learning technologies (defined later) individually and in combination provide potential solutions to scaling the use of AI in clinical care, ensuring data privacy, and supporting clinical data sharing for development and validation of novel algorithms. Edge computing allows for data processing close to the source of data acquisition and is particularly useful for near real-time data analysis and result generation, as well as preserving data privacy.[61] Many novel digital devices are now equipped with edge computational capabilities such as smartphones, smartwatches, and biometric sensors. Blockchains are digital records or databases in which multiple stakeholders have joint control of shared data, data transfer is encrypted to protect data privacy, and the system is essentially tamper proof.[62] Federated learning trains AI algorithms in a decentralized manner, thus ensuring data privacy because sensitive clinical data never leave the original location.[65] These options in addition to development of new methods to ensure effective data sharing while addressing privacy concerns will need to be incorporated into health care systems to allow patients to benefit equitably from AI algorithms.

REGULATORY APPROVAL OF ARTIFICIAL INTELLIGENCE– AND MACHINE LEARNING–BASED SOFTWARE AS A MEDICAL DEVICE

Any software "intended to treat, diagnose, cure, mitigate or prevent disease" is considered software as a medical device (SaMD) and classified based on associated clinical risk to patients and intended use.[66] The FDA's approval process for traditional medical devices was not originally designed for adaptive AI and ML technologies, and these technologies were initially being evaluated as static or "locked" algorithms (that do not change with time) using the SaMD framework, and any changes to the algorithm had to undergo premarket FDA review. However, a newer regulatory framework initially proposed in 2019 incorporates modifications to the AI/ML-based SaMD approval process. An action plan was also published in 2021 regarding the FDA's role in the development and regulation of AI/ML-based technologies[67] and highlighting key issues to consider, such as AI/ML best practices, including transparency, identification and mitigation of algorithmic bias, and real-world data collection/evaluation of model performance.[67] This document also acknowledges that with rapid advancements in AI/ML-based SaMD, its regulatory processes would need to evolve continuously. The European commission established an expert group to develop guidelines on trustworthy AI, which was published in 2019 and subsequently identified, based on feedback, that requirements related to transparency and human oversight were not explicitly covered in existing regulatory processes,[68] and steps were put in place to revise the guidelines. In keeping with the FDA, the European Commission also supports flexibility in the regulatory framework to allow for modifications as AI technologies evolve. The FDA has also partnered with Health Canada and the United Kingdom in establishing key guiding principles for good ML practice for medical device development.[69]

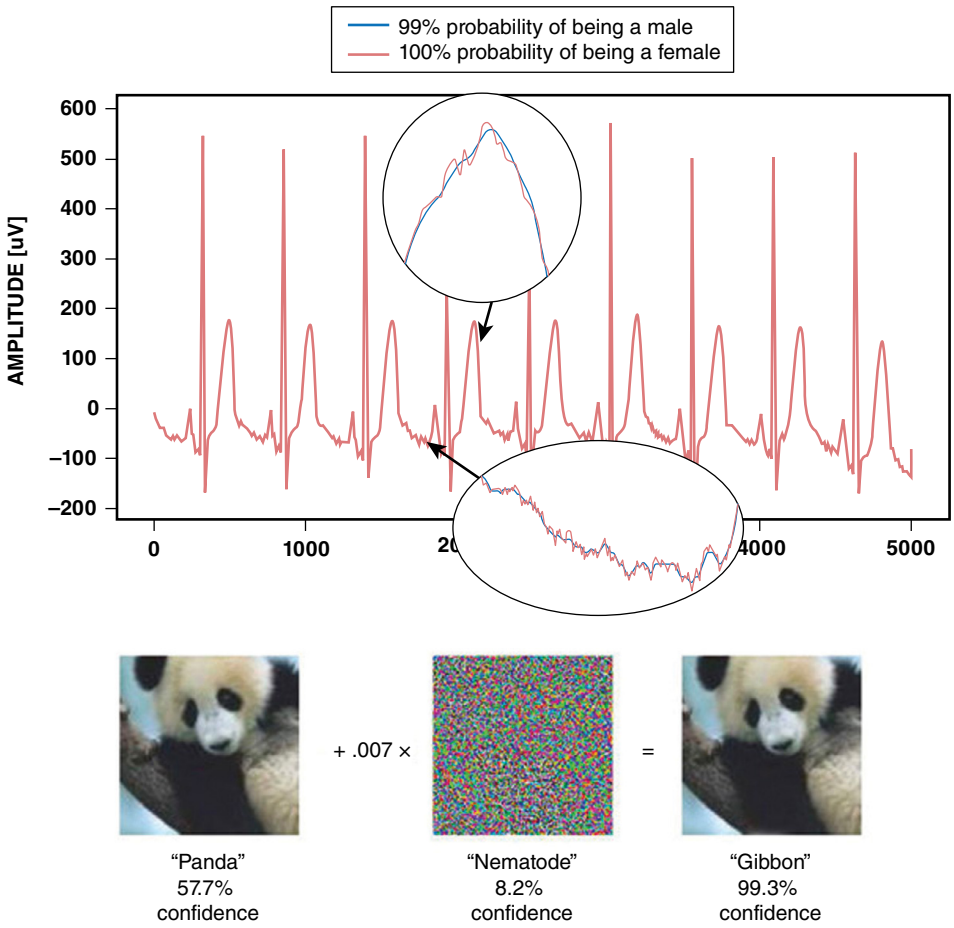
PITFALLS AND LIMITATIONS OF ARTIFICIAL INTELLIGENCE IN CARDIOVASCULAR MEDICINE

Despite the immense promise of ML, a number of considerations have impeded its development and require addressing. Before neural networks can be trained, data must be accessed in a usable format, and for many forms of ML, clearly labeled. This requires subject matter experts as well as technical experts. Data ownership remains an unresolved issue, particularly with patient data. Use of an individual's data in ML exposes them to risk of loss of privacy, and at the same time a third party may yield financial benefit, raising potential conflicts of interest. The training of many networks requires large quantities of data, often necessitating accumulation of data from more than a single institution, again with concerns relating to privacy and data ownership. There is currently a lack of well-established quality standards or a centralized clearinghouse for vetted technology.

Deep learning can make deep connections within data but can only learn from data that it encounters. Any preexisting biases or situations excluded from the training set may lead to unreliable results when fed into a clinically used network. Examples have included a higher rate of misidentification of Black versus White populations in facial recognition software. In the medical field, false associations could lead to a prediction of increased mortality because of zip code, socioeconomic status, and other nonmedical correlates.

Generative AI, a subset of AI models, has its own pitfalls. These models can sometimes produce "hallucinations," generating outputs that appear real but are incorrect. Even if a generative AI is set to only frame structures and incorporate user-input or trained data, such hallucinations might arise. This is especially problematic when the generated output seems convincing but is fundamentally flawed or baseless. Additionally, these models have debatable ability to de-identify themselves. Given their capacity to recall patterns, there's a tangible risk they might inadvertently memorize and reproduce specific training data, posing privacy concerns.

Neural networks have undergone adversarial attacks in which pixels are modified in an image with no visible effects to a human observer, yet with complete change in classification and network output (Fig. 10.4). Such attacks could lead to misclassification or misdiagnosis and raise questions about the lack of understanding of the mechanism of network classification.[70] This leads to the black box issue in that the components of a signal used by a network to make its determination are not known to humans, raising concerns about their broad-spread deployment. Careful clinical testing and vetting can mitigate this concern.



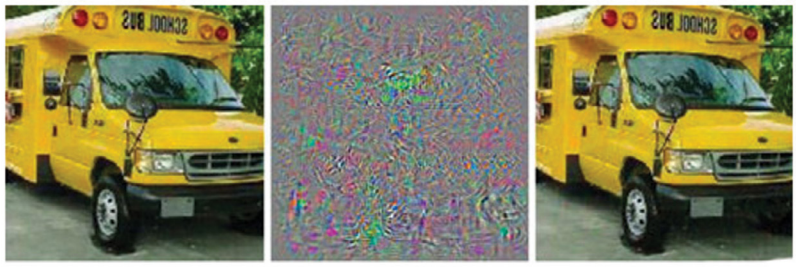


FIG. 10.4 Examples of adversarial attacks on neural networks. An electrocardiogram (ECG) *(blue tracing)* is correctly classified as being acquired from a male by a neural network. The addition of subclinical noise to the signal *(orange tracing)* leads the network to misclassify the tracing as belonging to a female, despite the absence of significant change to a human observer. The images *below* the ECG depict similar adversarial network attacks against a network designed for image classification. The addition of apparent noise results in no visible change to a human observer, but misclassification of a panda as a gibbon by the network, as well as a similar disruption using a different image.

The adoption of AI tools in clinical practice requires physician engagement and thoughtful assessment of workflow and implementation. Technology-driven solutions (e.g., many EMRs) in some cases have paradoxically led to physician burnout, resulted in patient dissatisfaction, and failed to fulfill their promise. Careful attention to user interfaces, patient and physician use requirements, meticulous validation, and outcomes-based observations will be essential to permit AI to improve clinical medicine. Early experience with large language models and their easy-to-use interactive nature hold promise for overcoming the user frustrations encountered with traditional systems, but their limitations (including hallucinations and occasional false information), are not fully addressed.

WEARABLES AND ARTIFICIAL INTELLIGENCE IN CARDIOVASCULAR MEDICINE

Wearable technologies (wearables) include a variety of electronic devices with sensor capabilities that can be worn on the limbs or torso (watches, rings, bands), affixed to the skin, or as apparel (garment or shoes)[71]; see eFig. 10.2). This approach permits continuous acquisition of large volumes of data, which are often acquired in noisy environments. AI inherently enables extraction of potentially clinically usable data. See the online version of this chapter for additional discussion on wearables and AI.

NEW DIRECTIONS

AI in CV medicine is poised to revolutionize the field in several promising directions. Numerous sources of physiologic signals can detect the earliest changes in physiology and homeostasis that have yet to be meaningfully tapped. Intrinsic signals include ECG, voice, sweat, static images, and video of various body parts (fundi, nail beds), whereas extrinsic signals include assessment of the energy that interacts with a body (e.g., ultrasound, CT, MRI, another human obtaining a history; Fig. 10.5). AI analysis has the most power when applied to raw, unprocessed data, as each step of the processing removes data before a

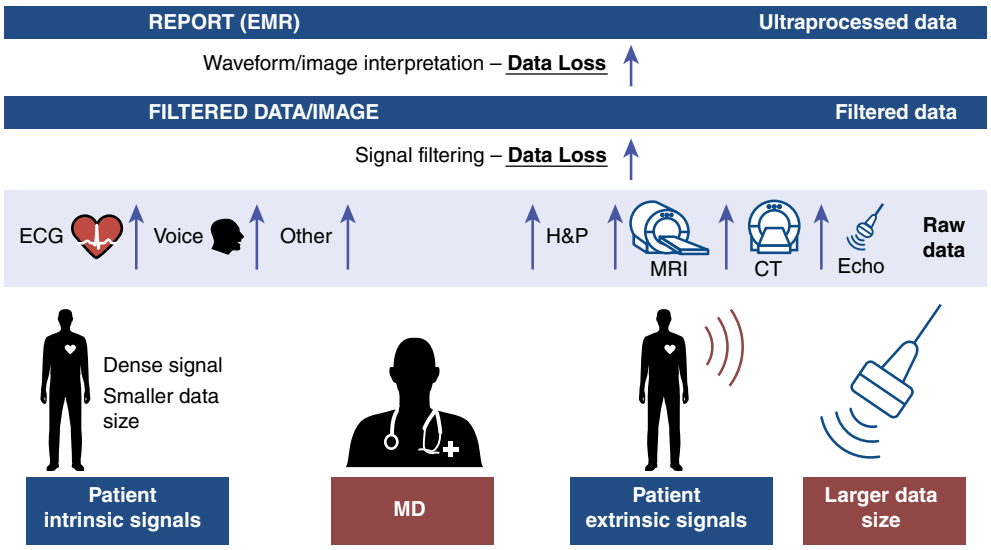


FIG. 10.5 Biologic signals that can be processed by artificial intelligence (AI) to extract meaningful medical information by AI tools. On the *left* are depicted intrinsic signals, those created by the human body, such as electrocardiogram *(ECG),* voice, and others (perspiration, eye motion, etc.). On the *right* are shown extrinsic signals, those generated by interrogating the human body with an energy form such as magnetic resonance imaging *(MRI)* computed tomography *(CT),* or echocardiogram *(Echo)* and analyzing those signals or by another human obtaining a history and making observations. Intrinsic signals tend to be more data dense and smaller, facilitating analysis, whereas extrinsic signals result in larger data size, but exquisite detail. Raw signals are filtered to create images, which are interpreted to generate reports. At each step, data are lost so that analysis of raw signals generally is more powerful than analysis of reports in the electronic medical record *(EMR). H&P,* History and physical examination.

report enters the EMR. Voice is a particularly rich signal, because its generation depends on innervation, vascular supply, lung function, and the synthesis of multiple systems. Early findings indicate voice analysis detects coronary artery disease, pulmonary hypertension, and AF, among other conditions. Voice includes language-dependent (meaning of the words a person is speaking) and language-independent (cepstral analysis) components, both of which are rich in physiologic data.[72] In aggregate AI, application to these signals enables exquisite phenotyping to further support early disease detection and genetic analysis.

Large language models can capture vast troves of information and respond to queries. These can be coupled to voice information, but also fundamentally transform a patient's and clinician's interaction with the EMR, and aid in rapid acquisition, identification, and assessment of specific medical knowledge. Patients will be greatly empowered to understand their disease and rely on clinicians for judgment, experience, empathy, and human touch to a greater extent. Patient reliance on a clinician's detailed medical knowledge of every available therapy may be mitigated. Their effective use in medicine requires elimination of hallucinations as described previously.[59] These efforts remain early.

Integration of current AI, new physiologic signals, large language models, and wearable sensors stands poised to transform medicine from episodic evaluations of disease to continuous assessment of health and changes in homeostatic physiology. These tools are already starting to empower personalized medicine, by providing rich and deep phenotyping, to better allow interpretation of genotype. The application of AI to genetic information is in its infancy.

Furthermore, AI is expected to enhance predictive modeling in cardiology, allowing for better risk stratification and prevention strategies. By analyzing large datasets, AI can identify patterns and predict the likelihood of future cardiac events, aiding in preventive care and resource allocation. Additionally, the integration of AI with wearable technology will enable continuous monitoring of patients' cardiac health, providing real-time data that can inform prompt adjustment of treatments. Overall, the incorporation of AI into CV medicine promises to enhance patient care, improve health outcomes, and streamline health care delivery. But challenges remain, as noted previously, including data privacy, potential errors, patient access, regulatory approaches and prospective assessment of these powerful new tools. They stand poised to change how health care is delivered, challenge the traditional roles of the physician and patient, affect reimbursement, and influence what resources are required, introducing great hope but also uncertainty and rapid change.

CONCLUSIONS

In summary, the application of ML to physiologic data promises to transform the practice of medicine. Many AI algorithms will be integrated into devices used by clinicians (including the EMR); others may be stand-alone tools. Although AI is unlikely to replace physicians, physicians who use ML tools will likely supplant those who do not. Much like the ECG at the turn of the century or the echocardiogram several decades ago, ML offers new ways to peer into the body to assess its current state, more accurately gauge its future state, and thus work to improve the human condition. The use of earlier disease detection using AI-empowered tools embedded in clinical and nonclinical environments, coupled with striking advances in therapies that modify risk factors and treat disease promise to bend the arc of CV morbidity and mortality and have an impact on human longevity. But substantial work remains to confirm, vet, and validate these powerful new tools and to update and vitalize the regulatory, societal, privacy, and economic implications of their implementation.

REFERENCES

Background

1. Lopez-Jimenez F, Attia Z, Arruda-Olson AM, *et al.* Artificial intelligence in cardiology: present and future. *Mayo Clin Proc.* 2020;95:1015–1039.
2. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature.* 2015;521:436–444.

ECG-Based Screening, Detection, and Prevention

3. Pipberger HV, Freis ED, Taback L, Mason HL. Preparation of electrocardiographic data for analysis by digital electronic computer. *Circulation.* 1960;21:413–418.
4. Caceres C A, Rikli AE. The digital computer as an aid in the diagnosis of cardiovascular disease. *Trans N Y Acad Sci.* 1961;23:240–245.
5. Caceres CA, Steinberg CA, Abraham S, *et al.* Computer extraction of electrocardiographic parameters. *Circulation.* 1962;25:356–362.
6. Rikli AE, Tolles WE, Steinberg CA, et al. Computer analysis of electrocardiographic measurements. *Circulation.* 1961;24:643–649.
7. Hannun AY, Rajpurkar P, Haghpanahi M, *et al.* Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. *Nat Med.* 2019;25:65–69.
8. Ribeiro AH, Horta Ribeiro M, Paixão GMM, *et al.* Automatic diagnosis of the 12-lead ECG using a deep neural network. *Nat Commun.* 2020;11:1760.
9. Smith SW, Walsh B, Grauer K, *et al.* A deep neural network learning algorithm outperforms a conventional algorithm for emergency department electrocardiogram interpretation. *J Electrocardiol.* 2019;52:88–95.
10. Halcox JPJ, Wareham K, Cardew A, et al. Assessment of remote heart rhythm sampling using the AliveCor Heart Monitor to screen for atrial fibrillation: the REHEARSE-AF Study. *Circulation.* 2017;136:1784–1794.
11. Rajakariar K, Koshy AN, Sajeev JK, et al. Accuracy of a smartwatch based single-lead electrocardiogram device in detection of atrial fibrillation. *Heart.* 2020;106:665–670.

12. Wasserlauf J, You C, Patel R, et al. Smartwatch performance for the detection and quantification of atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2019;12:e006834.
13. Perez MV, Mahaffey KW, Hedlin H, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med.* 2019;381:1909–1917.
14. Chung EH, Guise KD. QTC intervals can be assessed with the AliveCor heart monitor in patients on dofetilide for atrial fibrillation. *J Electrocardiol.* 2015;48:8–9.
15. Samol A, Bischof K, Luani B, et al. Single-lead ECG recordings including Einthoven and Wilson leads by a smartwatch: a new era of patient directed early ECG differential diagnosis of cardiac diseases? *Sensors (Basel).* 2019;19:4377.
16. Ferdman DJ, Liberman L, Silver ES. A smartphone application to diagnose the mechanism of pediatric supraventricular tachycardia. *Pediatr Cardiol.* 2015;36:1452–1457.
17. Attia ZI, Kapa S, Lopez-Jimenez F, et al. Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram. *Nat Med.* 2019;25:70–74.
18. Attia ZI, Noseworthy PA, Lopez-Jimenez F, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet.* 2019;394:861–867.
19. Ko WY, Siontis KC, Attia ZI, et al. Detection of hypertrophic cardiomyopathy using a convolutional neural network-enabled electrocardiogram. *J Am Coll Cardiol.* 2020;75:722–733.
20. Kwon JM, Jeon KH, Kim HM, et al. Comparing the performance of artificial intelligence and conventional diagnosis criteria for detecting left ventricular hypertrophy using electrocardiography. *Europace.* 2020;22:412–419.
21. Galloway CD, Valys AV, Shreibati JB, et al. Development and validation of a deep-learning model to screen for hyperkalemia from the electrocardiogram. *JAMA Cardiol.* 2019;4:428–436.
22. Attia ZI, Friedman PA, Noseworth PA, et al. Age and sex estimation using artificial intelligence from standard 12-lead ECGs. *Circ Arrhythm Electrophysiol.* 2019;12:e007284.
23. Cohen-Shelly M, Arria ZI, Friedman PA, et al. Electrocardiogram screening for aortic valve stenosis using artificial intelligence. *Eur Heart J.* 2021;42:2885–2896.
24. Sawano S, Kodera S, Katsushika S, et al. Deep learning model to detect significant aortic regurgitation using electrocardiography. *J Cardiol.* 2022;79:334–341.
25. Awasthi S, Sachdevi N, Gupta Y, et al. Identification and risk stratification of coronary disease by artificial intelligence-enabled ECG. *EClinicalMedicine.* 2023;65:102259.
26. Bachtiger P, Petri CF, Scott FE, et al. Point-of-care screening for heart failure with reduced ejection fraction using artificial intelligence during ECG-enabled stethoscope examination in London, UK: a prospective, observational, multicentre study. *Lancet Digit Health.* 2022;4:e117–e125.
27. Yao X, McCoy RG, Friedman PA, et al. Clinical trial design data for electrocardiogram artificial intelligence-guided screening for low ejection fraction (EAGLE). *Data Brief.* 2020;28:104894.
28. Yao X, Rushlow DR, Inselman JW, et al. Artificial intelligence-enabled electrocardiograms for identification of patients with low ejection fraction: a pragmatic, randomized clinical trial. *Nat Med.* 2021;27:815–819.
29. Attia ZI, Dugan J, Rideout A, et al. Automated detection of low ejection fraction from a one-lead electrocardiogram: application of an AI algorithm to an electrocardiogram-enabled Digital Stethoscope. *Eur Heart J Digit Health.* 2022;3:373–379.
30. Attia, Z. I., Harmon DM, Dugan J, et al. Prospective evaluation of smartwatch-enabled detection of left ventricular dysfunction. *Nat Med.* 2022;28:2497–2503.
31. Noseworthy PA, Attia ZI, Behnken EM, et al. Artificial intelligence-guided screening for atrial fibrillation using electrocardiogram during sinus rhythm: a prospective non-randomised interventional trial. *Lancet.* 2022;400:1206–1212.
32. Tison GH, Siontios KC, Abreau S, et al. Assessment of disease status and treatment response with artificial intelligence-enhanced electrocardiography in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2022;79:1032–1034.
33. Adedinsewo DA, Johnson PW, Douglass EJ, et al. Detecting cardiomyopathies in pregnancy and the postpartum period with an electrocardiogram-based deep learning model. *Eur Heart J Digit Health.* 2021;2:586–596.

Artificial Interpretation in Image Interpretation

34. Blaivas M, Adhikari S, Savitsky EA, Blaivas LN, Liu YT. Artificial intelligence versus expert: a comparison of rapid visual inferior vena cava collapsibility assessment between POCUS experts and a deep learning algorithm. *J Am Coll Emerg Physicians Open.* 2020;1:857–864.
35. Motazedian P, Marbach JA, Prosperi-Poerta G, *et al.* Diagnostic accuracy of point-of-care ultrasound with artificial intelligence-assisted assessment of left ventricular ejection fraction. *NPJ Digit Med.* 2023;6:201.
36. Baum E, Tandel MD, Ren C, et al. Acquisition of cardiac point-of-care ultrasound images with deep learning: a randomized trial for educational outcomes with novices. *CHEST Pulm.* 2023;1:100023.
37. Otaki Y, Singh A, Kavanagh P, et al. Clinical deployment of explainable artificial intelligence of SPECT for diagnosis of coronary artery disease. *JACC Cardiovasc Imaging.* 2022;15:1091–1102.
38. Gomez J, Doukky R. Artificial intelligence in nuclear cardiology. *J Nucl Med.* 2019;60:1042–1043.
39. Zhou J, Du M, Chang S, Chen Z. Artificial intelligence in echocardiography: detection, functional evaluation, and disease diagnosis. *Cardiovasc Ultrasound.* 2021;19:29.
40. Asch FM, Descamps T, Sarwar R, et al. Human versus artificial intelligence-based echocardiographic analysis as a predictor of outcomes: an analysis from the World Alliance Societies of Echocardiography COVID Study. *J Am Soc Echocardiogr.* 2022;35:1226–1237.e1227.
41. Al Kindi D, Househ M, Alam T, Shah Z. Artificial intelligence models for heart chambers segmentation from 2D echocardiographic images: a scoping review. *Stud Health Technol Inform.* 2022;289:264–267.
42. Jiang B, Guo N, Ge Y, et al. Development and application of artificial intelligence in cardiac imaging. *Br J Radiol.* 2020;93:20190812.
43. Zhang Q, Burrage MK, Shanmuganathan M, et al. Artificial intelligence for contrast-free MRI: scar assessment in myocardial infarction using deep learning-based virtual native enhancement. *Circulation.* 2022;146:1492–1503.

Other Clinical Applications of Artificial Intellenge

44. Feeny AK, Chung MK, Madabhushi A, *et al.* Artificial intelligence and machine learning in arrhythmias and cardiac electrophysiology. *Circ Arrhythm Electrophysiol.* 2020;13:e007952.
45. Trayanova NA, Popescu DM, Shade JK. Machine learning in arrhythmia and electrophysiology. *Circ Res.* 2021;128:544–566.
46. Koifman E, Loevsky I, Feld Y, Roguin A. Automated fractional flow reserve assessment - artificial intelligence in the catheterization laboratory. *Cardiovasc Revasc Med.* 2022;38:127–128.
47. Sardar P, Abbott JD, Kunda A, et al. Impact of artificial intelligence on interventional cardiology: from decision-making aid to advanced interventional procedure assistance. *JACC Cardiovasc Interv.* 2019;12:1293–1303.
48. Wang DD, Qian Z, Vukicevic M, *et al.* 3D Printing, computational modeling, and artificial intelligence for structural heart disease. *JACC Cardiovasc Imaging.* 2021;14:41–60.
49. Maurya MR, Sahar Riyaz NUS, Sai Bhargava Reddy M, *et al.* A review of smart sensors coupled with internet of things and artificial intelligence approach for heart failure monitoring. *Med Biol Eng Comput.* 2021;59:2185–2203.
50. Juhn Y, Liu H. Artificial intelligence approaches using natural language processing to advance EHR-based clinical research. *J Allergy Clin Immunol.* 2020;145:463–469.
51. Zhuang XD, Tian T, Liao LZ, et al. Deep phenotyping and prediction of long-term cardiovascular disease: optimized by machine learning. *Can J Cardiol.* 2022;38:774–782.
52. Hill NR, Ayoubkhani D, McEwan P, *et al.* Predicting atrial fibrillation in primary care using machine learning. *PLoS One.* 2019;14:e0224582.

Artificial Intelligence and the Electronic Health Record

53. Liu H, Bielinski SJ, Sohn S, et al. An information extraction framework for cohort identification using electronic health records. *AMIA Jt Summits Transl Sci Proc.* 2013;2013:149–153.
54. Upadhyaya SG, Murphree DH, Ngufor CG, et al. Automated diabetes case identification using electronic health record data at a tertiary care facility. *Mayo Clin Proc Innov Qual Outcomes.* 2017;1:100–110.
55. Afzal N, Sohn S, Abram S, et al. Mining peripheral arterial disease cases from narrative clinical notes using natural language processing. *J Vasc Surg.* 2017;65:1753–1761.
56. Kirby JC, Speltz P, Rasmussen LV, et al. PheKB: a catalog and workflow for creating electronic phenotype algorithms for transportability. *J Am Med Inform Assoc.* 2016;23:1046–1052.
57. De Freitas JK, Johnson KW, Golden E, *et al.* Phe2vec: automated disease phenotyping based on unsupervised embeddings from electronic health records. *Patterns (N Y).* 2021;2:100337.

Integration of Artificial Intelligence Into Practice: Progress, Challenges, and Caveats

58. He B, Kwan AC, Cho JH, et al. Blinded, randomized trial of sonographer versus AI cardiac function assessment. *Nature.* 2023;616:520–524.
59. Siontis KC, Noseworthy PA, Attia ZI, Friedman PA. Artificial intelligence-enhanced electrocardiography in cardiovascular disease management. *Nat Rev Cardiol.* 2021;18:465–478.
60. He J, Baxter SL, Xu J, et al. The practical implementation of artificial intelligence technologies in medicine. *Nat Med.* 2019;25:30–36.
61. Chen J, Ran X. Deep learning with edge computing: a review. *Proc IEEE.* 2019;107:1655–1674.
62. Ng WY, Tan TE, Movva PVH, et al. Blockchain applications in health care for COVID-19 and beyond: a systematic review. *Lancet Digit Health.* 2021;3:e819–e829.
63. Deleted in review.
64. Deleted in review.
65. Rehman A, Abbas S, Khan MA, et al. A secure healthcare 5.0 system based on blockchain technology entangled with federated learning technique. *Comput Biol Med.* 2022;150:106019.
66. US Food and Drug Administration. *Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD).* Washington, DC: FDA; n.d.
67. US Food and Drug Administration. *Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan.* Washington, DC: FDA; 2021.
68. European Commission on Artificial Intelligence. *A European Approach to Excellence and Trust.* Brussels: European Commisson; 2020.
69. US Food and Drug Administration. *Good Machine Learning Practice for Medical Device Development: Guiding Principles.* Washington, DC: FDA; 2021.

Wearable Devices in Cardiovascular Medicine

70. Han X, Hu Y, Foschini L, et al. Deep learning models for electrocardiograms are susceptible to adversarial attack. *Nat Med.* 2020;26:360–363.
71. Bayoumy K, Gaber M, Elshafeey A, et al. Smart wearable devices in cardiovascular care: where we are and how to move forward. *Nat Rev Cardiol.* 2021;18:581–599.
72. Golovchiner G, Glikson M, Swissa M, et al. Automated detection of atrial fibrillation based on vocal features analysis. *J Cardiovasc Electrophysiol.* 2022;33:1647–1654.
73. Ferguson T, Olds T, Curtis R, et al. Effectiveness of wearable activity trackers to increase physical activity and improve health: a systematic review of systematic reviews and meta-analyses. *Lancet Digit Health.* 2022;4:e615–e626.
74. Szeto K, Arnold J, Singh B, et al. Interventions using wearable activity trackers to improve patient physical activity and other outcomes in adults who are hospitalized: a systematic review and meta-analysis. *JAMA Netw Open.* 2023;6:e2318478.
75. Williams GJ, Al-Baraikan A, Rademakders FE, et al. Wearable technology and the cardiovascular system: the future of patient assessment. *Lancet Digit Health.* 2023;5:e467–e476.
76. Zepeda-Echavarria A, van de Leur R, van Sleuwen M, et al. Electrocardiogram devices for home use: technological and clinical scoping review. *JMIR Cardio.* 2023;7:e44003.
77. Al-Alusi MA, Ding E, McManus DD, Lubitz SA. Wearing your heart on your sleeve: the future of cardiac rhythm monitoring. *Curr Cardiol Rep.* 2019;21:158.
78. Castaneda D, Esparza A, Ghamari M, Soltanpur C, Nazeran H. A review on wearable photoplethysmography sensors and their potential future applications in health care. *Int J Biosens Bioelectron.* 2018;4:195–202.
79. Charlton PH, Kyriaco PA, Mant J, *et al.* Wearable photoplethysmography for cardiovascular monitoring. *Proc IEEE Inst Electr Electron Eng.* 2022;110:355–381.
80. Allen J, Kyriaco PA, eds. *Photoplethysmography: Technology, Signal Analysis, and Applications.* New York: Academic Press; 2021.
81. Alkhodari M, Fraiwan L. Convolutional and recurrent neural networks for the detection of valvular heart diseases in phonocardiogram recordings. *Comput Methods Programs Biomed.* 2021;200:105940.
82. Krittanawong C, Rogers AJ, Johnson KW, et al. Integration of novel monitoring devices with machine learning technology for scalable cardiovascular management. *Nat Rev Cardiol.* 2021;18:75–91.
83. Wang C, Li X, Hu H, et al. Monitoring of the central blood pressure waveform via a conformal ultrasonic device. *Nat Biomed Eng.* 2018;2:687–695.
84. Lai J, Tan H, Wang J, *et al.* Practical intelligent diagnostic algorithm for wearable 12-lead ECG via self-supervised learning on large-scale dataset. *Nat Commun.* 2023;14:3741.
85. Hutton J, Lingawi S, Puyat JH, et al. Sensor technologies to detect out-of-hospital cardiac arrest: a systematic review of diagnostic test performance. *Resusc Plus.* 2022;11:100277.
86. Chen E, Jiang G, Su R, et al. A new smart wristband equipped with an artificial intelligence algorithm to detect atrial fibrillation. *Heart Rhythm.* 2020;17:847–853.
87. Tison GH, Sanchez JM, Ballinger B, et al. Passive detection of atrial fibrillation using a commercially available smartwatch. *JAMA Cardiol.* 2018;3:409–416.
88. Stehlik J, Schmallfuss C, Bozkurt B, et al. Continuous wearable monitoring analytics predict heart failure hospitalization: The LINK-HF Multicenter Study. *Circ Heart Fail.* 2020;13:e006513.
89. Inan OT, Pouyan MB, Javaid AQ, *et al.* Novel wearable seismocardiography and machine learning algorithms can assess clinical status of heart failure patients. *Circ Heart Fail.* 2018;11:e004313.
90. Chorba JS, Shapiro AM, Le L, et al. Deep learning algorithm for automated cardiac murmur detection via a digital stethoscope platform. *J Am Heart Assoc.* 2021;10:e019905.
91. Lv J, Dong B, Lei H, et al. Artificial intelligence-assisted auscultation in detecting congenital heart disease. *Eur Heart J Digit Health.* 2021;2:119–124.
92. Thompson WR, Reinisch AJ, Unterberger MJ, Schriefl AJ. Artificial intelligence-assisted auscultation of heart murmurs: validation by virtual clinical trial. *Pediatr Cardiol.* 2019;40:623–629.
93. Li XC, Liu XH, Liu LB, et al. Evaluation of left ventricular systolic function using synchronized analysis of heart sounds and the electrocardiogram. *Heart Rhythm.* 2020;17:876–880.
94. Lee SH, Kim YS, Yeo MK, *et al.* Fully portable continuous real-time auscultation with a soft wearable stethoscope designed for automated disease diagnosis. *Sci Adv.* 2022;8:eabo5867.