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ROLE OF ARTIFICIAL INTELLIGENCE-ENHANCED ELECTROCARDIOGRAPHY IN CARDIOVASCULAR DISEASE MANAGEMENT: WHERE WE ARE HEADING.

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INTRODUCTION

Over the last decade, research on AI in medicine and biomedicine and the number of publications in these fields have substantially increased. Research has come up with promising AI developments in general machine learning (ML) algorithms, for manifold applications to predict clinical events, to improve diagnoses accuracy as well as treatments, and to reduce the burden of disease.

While a balance between the increasing amount of documented data on the one hand and the demographic change and aging populations on the other hand challenges our health care systems, big data and artificial intelligence (AI) in medicine offer a huge potential to relieve physicians from the increasing complexity of today's health care and information overload when treating patients.

Cardiac amyloidosis (CA), once thought to be rare and universally fatal, is now recognized as an important cause of heart failure, particularly in patients with preserved ejection fraction. Advances in therapy have led to significant improvement in outcomes, but survival is hindered by life-threatening delays in diagnosis. Whereas more than 30 proteins may misfold to cause amyloidosis, main types involve the heart: light chain associated amyloid (AL), due to a clonal plasma cell disorder of the bone marrow; and transthyretin amyloid (ATTR), related to misfolding of transthyretin produced by the liver result from either an inherited mutation in the transthyretin gene (ATTRv) or from "wild-type" (genetically normal) transthyretin deposition (ATTRwt). Treatment is available for both AL and ATTR amyloidosis and is rapidly improving. If it is untreated, cardiac AL amyloidosis is rapidly progressive and fatal.

Patients with systemic amyloidosis are commonly evaluated by multiple providers before the diagnosis is established, often requiring travel to a national center. Early symptoms may be vague and attributed to other causes, requiring a high index of suspicion. Whereas advances in cardiac imaging have improved the diagnosis, classic findings are not always present or may go unrecognized, especially if amyloidosis has not been suggested by the referring provider. As cardiac involvement in systemic amyloidosis is the most important determinant of survival, there is a critical need for early diagnosis to promote timely and effective therapy.

Electrocardiogram (ECG)

The electrocardiogram (ECG) is a ubiquitous tool in clinical medicine that has been used by cardiologists and non-cardiologists for decades.

Although the acquisition of the ECG recording is well standardized and reproducible, the reproducibility of human interpretation of the ECG varies greatly according to levels of experience and expertise.

This transformative progress has not occurred without potential limitations and challenges that require attention. Challenges with AI applications are not necessarily unique to the ECG and include the need for data quality control, external validity, data security and the demonstration of superior patient outcomes with the implementation of AI-enabled tools, such as the AI–ECG.

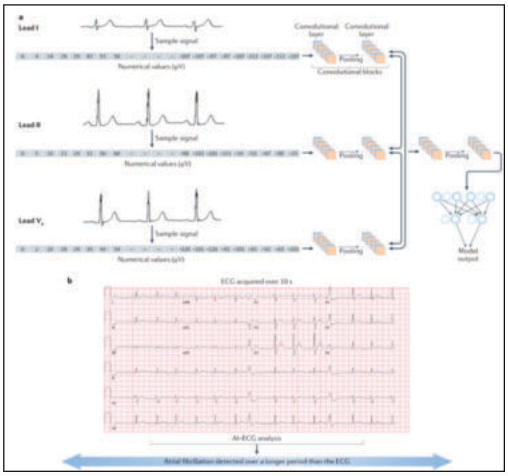
Deep-learning methods applied to the ECG

Deep learning is a subfield of machine learning that uses neural networks with many layers (hence the term 'deep') to learn a function between a set of inputs and a set of outputs.

The strength of deep neural networks lies in using their ability to identify novel relationships in the data independent of features selected by a human.[1-2]

The agnostic approach in a neural network is an optimal representation, but this approach is also non-linear, and the learned associations between input and output data are unexplainable at present, making the model a black box — humans cannot understand how the network makes its decisions- which is one of the concerns raised regarding the clinical application of deep-learning CNNs. Therefore, less agnostic machine-learning models, such as the more traditional logistic regression, reinforcement learning and random forest models, still hold promise and can help to inform research and clinical practice. For example, reinforcement learning is a field of AI providing the framework for training of a clinical decision model in which certain decisions (model input) under specific conditions are linked to long-term outcomes.

Fig. 1: Development of a convolutional neural network using the 12-lead ECG and application to detect silent atrial fibrillation.



Fully automated interpretation of ECGs

One of the top priorities for the application of AI to the interpretation of ECGs is the creation of comprehensive, human-like interpretation capability. Since the advent of the digital ECG more than 60 years ago[3]4, ongoing effort has been towards rapid, high-quality and comprehensive computer-generated interpretation of the ECG. The problem seems tractable; after all, ECG interpretation is a fairly circumscribed application of pattern recognition to a finite dataset. Early programs for the interpretation of digital ECGs could easily recognize fiducial points, make discrete measurements and define common quantifiable abnormalities5-7. Modern technologies have moved beyond these rule-based approaches to recognize patterns in massive quantities of labelled ECG data8,9.

Several groups have worked to create AI-driven algorithms, and some of these algorithms are already in limited clinical use10. Some studies have developed CNNs from large datasets of single-lead ECGs and then applied them to the 12-lead ECG. For instance, using 2 million labelled single-lead ECG traces collected in the Clinical Outcomes in Digital Electrocardiology study, one group used a CNN to identify six types of abnormalities on the 12-lead ECG9. This study demonstrated the feasibility of this approach, but widespread implementation or external validation in other 12-lead ECG datasets is forthcoming. Another group conducted a similar study of the application of CNNs to single-lead ECGs and demonstrated that the CNN could outperform practising cardiologists for some diagnoses8.

In an evaluation published in 2020, a CNN was developed for the multilabel diagnosis of 21 distinct heart rhythms based on the 12-lead ECG using a training and validation dataset of >80,000 ECGs from >70,000 patients11. The reference standard consisted of consensus labels by a committee of cardiologists. In a test dataset of 828 ECGs, the optimal network exactly matched the gold standard labels in 80% of the ECGs, significantly exceeding the performance of a single cardiologist interpreter 12.

This technology will be particularly important as we increasingly rely on ECG data obtained through novel, consumer-facing applications, which are massively scalable. For instance, AI–ECG algorithms have been applied to single-lead ECG traces obtained through mobile, smartwatch-enabled recordings for the detection of AF13[-14]

Nevertheless, although great progress has been made towards a comprehensive, human-like ECG-interpretation package, the realization remains on the horizon. Even in its most modern incarnation, the package lacks the accuracy needed for implementation without human oversight15. Additionally, computer-derived ECG interpretation has the potential to influence human over-readers and, if inaccurate, can serve as a source of bias or systematic error.

The ECG as a deep phenotyping tool

Interpretation of an ECG by a trained cardiologist relies on established knowledge of what is normal or abnormal on the basis of more than a century of experience with assessing the ECG in patient care and based on our understanding of the electropathophysiology of various cardiac conditions. Despite the enormous potential to gain insights into cardiac health and disease from an expert interpretation of the ECG, the information gain is limited by the interpreter's finite ability to detect isolated characteristics or patterns fitting established rules. However, hidden in plain sight might be subtle signals and patterns that do not fit traditional knowledge and that are unrecognizable by the human eye. Harnessing the power of deep-learning AI techniques together with the availability of large ECG and clinical datasets, developing tools for systematic extraction of features of ECGs and their association with specific cardiac diagnoses has become feasible. Of course, some conditions are not reflected in the ECG, which even an AI–ECG cannot resolve — even if these technologies can see beyond an expert reader's capacity, they cannot see what is not there. In this section, we review the latest advances in the application of deep-learning AI techniques to the 12-lead ECG for the detection of asymptomatic cardiovascular disease that might not be readily apparent, even to expert eyes.

Detection of LV systolic dysfunction

The systolic function of the left ventricle, traditionally quantified as the LVEF by echocardiography, is a key measure of cardiac function. A reduced LVEF defines a large subgroup of patients with heart failure, but a decline in LVEF can be asymptomatic for a long time before any symptoms trigger evaluation. Indeed, up to 6% of people in the community might have asymptomatic LV dysfunction (LVEF <50%)16. A low LVEF has both prognostic and management implications17. Detection of a low LVEF should trigger a thorough evaluation for any reversible causes that should be addressed in a timely fashion to minimize the extent of permanent myocardial damage. The early initiation of optimal medical therapy can result in improvements in systolic LV function and quality of life, but can also reduce heart failure-related morbidity and mortality18.

The potential of the AI–ECG as a marker of asymptomatic LV dysfunction has been demonstrated. With the use of linked ECG and echocardiographic data from 44,959 patients at the Mayo Clinic (Rochester, MN, USA), a CNN was trained to identify patients with LV dysfunction, defined as LVEF of ≤35% by echocardiography, on the basis of the ECG alone[19-25]

Detection of silent AF from a sinus-rhythm ECG

AF portends an increased risk of impaired quality of life, stroke and heart failure, and results in frequent visits to the emergency department and frequent inpatient admissions. Among patients with an embolic stroke of undetermined source (ESUS), previously called 'cryptogenic stroke', who undergo 30-day rhythm monitoring, about 15% are found to have previously undiagnosed paroxysmal AF26. In these patients, anticoagulation lowers the recurrence of stroke and might lower mortality, whereas in the absence of documented AF, anticoagulation offers no clinical benefit and increases the risk of bleeding27 28. However, the diagnosis of AF can be elusive because up to 20% of patients are completely asymptomatic, and another approximately one-third of patients have atypical symptoms29. Moreover, AF is only intermittent (or paroxysmal) in many patients. Despite extensive research on the topic, the value of screening individuals for AF remains a matter of debate, and the US Preventive Services Task Force states that the data are currently insufficient to recommend routine AF screening in general populations30.

In the recent Apple Heart Study31, the largest pragmatic evaluation of AF screening in a general population using a smartwatch-enabled photoplethysmography technology, 0.52% of participants received notifications of possible AF over an average of >3 months of monitoring.

Patients with at least one ECG showing AF within 31 days after the sinus-rhythm ECG were classified as being positive for AF. In the testing dataset, the algorithm demonstrated an AUC of 0.87, sensitivity of 79.0%, specificity of 79.5% and an accuracy of 79.4% in detecting patients with documentation of AF using only information from the sinus-rhythm ECG32,Additionally, this tool can be applied retroactively to digitally stored ECGs from patients with a previous ESUS. This algorithm might facilitate targeted AF surveillance (such as using an ambulatory rhythm-monitoring patch or implantable loop recorder) in subsets of high-risk patients. This work is preliminary, but we are currently assessing the performance of this algorithm in identifying patients who might benefit from prospective AF screening or monitoring (with Holter or extended monitoring) and, ultimately, various stroke-prevention strategies. We also note that other groups have derived similar AF risk-prognostication tools that examine other electrophysiological parameters, such as signal-averaged ECG-derived P-wave analysis33-[34].

AI-enabled ECG and rhythm tools in AF care

In addition to screening individuals for silent AF, CNNs can also be developed from ECGs or other rhythm-monitoring data (including those derived from permanently implanted cardiac devices) for the stratification of stroke risk and the refinement of decision-making about oral anticoagulant use. In an analysis using data from implanted cardiac devices in >3,000 patients with AF (including 71 patients with stroke), three different supervised machine-learning models of AF burden signatures were developed to predict the risk of stroke (random forest, CNN and L1 regularized logistic regression)35. In the testing cohort, the random forest model had an AUC of 0.66, the CNN model had an AUC of 0.60 and the L1 regularized logistic regression model had an AUC of 0.56. By contrast, the CHA_2DS_2–VASc score, the most widely used stroke-prediction scheme in current practice36, had an AUC of 0.52 for stroke prediction. However, the highest AUC (0.63) was achieved when the CHA_2DS_2–VASc score was combined with the random forest and CNN models35, indicating the prognostic strength of approaches that combine AI-enriched models with traditional clinical tools. The performance of this model is still quite modest. The integration of additional information from the clinical history, imaging tests and circulating biomarkers might further improve risk stratification but this task is beyond current AI capabilities. For example, in an unsupervised cluster analysis of approximately 10,000 patients with AF in the ORBIT-AF registry, including patient-specific clinical data, medications, and laboratory, ECG and imaging data, four clinically relevant phenotypes of AF were identified, each with distinct associations with clinical outcomes (low comorbidity, behavioural comorbidity, device implantation and atherosclerotic comorbidity clusters)37. However, although this finding offers a proof of concept, the clinical utility of these clusters has not yet been demonstrated. The hope is that phenotype-specific treatment strategies will lead to superior patient outcomes, but testing is required.

Detection of HCM

HCM is infrequent in the general population, with an estimated prevalence of 1 in 200 to 1 in 500 individuals38,39. However, HCM is one of the leading causes of sudden cardiac death among adolescents and young adults. HCM is also associated with substantial morbidity in all age groups40.

In most cases, a diagnosis of HCM can be established with echocardiography combined with the clinical history, but the widespread use of echocardiography for the detection of HCM in otherwise asymptomatic individuals is impractical. Therefore, alternative modalities, such as the ECG, have been considered as a means for screening. More than 90% of patients with HCM have electrocardiographic abnormalities41, but these abnormalities are non-specific and can be indistinguishable from LV hypertrophy. Generally, ECG screening has relied on manual or automated detection of particular features, such as LV hypertrophy, left axis deviation, prominent Q waves and T-wave inversions. However, these approaches have insufficient diagnostic performance to justify routine ECG screening42. Moreover, several sets of ECG criteria have been proposed to distinguish between HCM and athletic heart adaptation, but their diagnostic performance has been inconsistent when external validations have been attempted43,44. The nature of a deep-learning AI approach might offer the advantage of an agnostic and unbiased approach to the ECG-based detection of HCM that does not rely on traditional criteria for LV hypertrophy.

With use of the ECGs of 2,500 patients with a validated diagnosis of HCM and >50,000 age-matched and sex-matched control individuals without HCM, an AI–ECG CNN was trained and validated to diagnose HCM on the basis of the ECG alone45. In an independent testing cohort of 612 patients with HCM and 12,788 control individuals, the AUC of the CNN was 0.96 (95% CI 0.95–0.96) with sensitivity of 87% and specificity of 90%. The performance of the model was robust in subgroups of patients meeting the ECG criteria for LV hypertrophy and among those with normal ECGs45. Importantly, performance was even better in younger patients (aged <40 years) but declined with increasing age. Furthermore, the performance of the model did not seem to be affected by the sarcomeric mutation status of the patient, given that the model-derived probabilities for a diagnosis of HCM were a median of 97% and 96% in patients with HCM who either had or did not have confirmed variants in sarcomere-encoding genes, respectively45. The algorithm developed had equally favourable performance when implemented on the basis of a single lead (rather than all 12 leads of the ECG), meaning that this algorithm could be applied as a screening test on a large scale and across various resource settings.

Another group of investigators used a large, 12-lead ECG dataset to train machine-learning models for the detection of HCM together with other elements of cardiac structure (LV mass, left atrial volume and early diastolic mitral annulus velocity) and disease (pulmonary arterial hypertension, cardiac amyloidosis and mitral valve prolapse)46.(Fig 2)

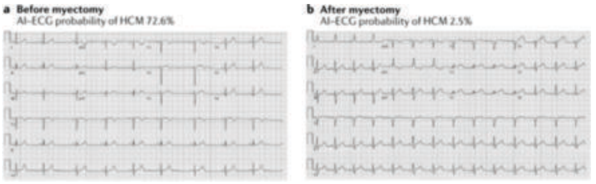


Fig. 2: The AI–ECG to detect HCM.

*Use of an artificial intelligence-enhanced electrocardiogram (AI–ECG) model to detect obstructive hypertrophic cardiomyopathy (HCM) in a woman aged 21 years before (part **a**) and after (part **b**) septal myectomy.*

Detection of hyperkalaemia

Numerous studies have shown that either hyperkalaemia or hypokalaemia is associated with increased mortality, and evidence suggests that the mortality associated with hyperkalaemia might be linked to underdosing of evidence-based therapies47. Our group has evaluated the performance of an AI–ECG CNN for the detection of hyperkalaemia in patients with chronic kidney disease48,49. In the latest large-scale evaluation, the model was trained to detect serum potassium levels of ≥5.5mmol/l using >1.5 million ECGs from nearly 450,000 patients who underwent contemporaneous assessment of serum potassium levels. This level of potassium was chosen because this threshold was thought to be clinically actionable. At this cut-off point, the model demonstrated 90% sensitivity and 89% sensitivity in a multicentre, external validation cohort49.

Antiarrhythmic drug management

Dofetilide and sotalol are commonly used for the treatment of AF. Their antiarrhythmic effect is exerted on the myocardium by prolonging the duration of the repolarization phase, meaning that QT prolongation is an anticipated effect of these drugs. Owing to the ensuing risk of substantial QT prolongation and potentially fatal ventricular proarrhythmia, patients require close monitoring with a continuous ECG in the hospital setting when these drugs are used, particularly for dofetilide. In addition, with the long-term use of these medications, the QT interval should be intermittently assessed because dose adjustments might be necessary in cases of substantial QT prolongation, concomitant medications with QT-prolonging effects and fluctuations in renal function (both sotalol and dofetilide are primarily metabolized through the kidneys). Using serial 12-lead ECGs and linked information on plasma dofetilide concentrations in 42 patients who were treated with dofetilide or placebo in a crossover randomized clinical trial, a deep-learning algorithm predicted plasma dofetilide concentrations with good correlation (r=0.85)50. By comparison, a linear model of the corrected QT interval correlated with dofetilide concentrations with a coefficient of 0.64 (ref.50). This finding suggests that the QT interval might not accurately reflect the plasma dofetilide concentration in some patients and so might underestimate or overestimate the proarrhythmic risk. Machine-learning approaches, including supervised, unsupervised and reinforcement learning, have also been used to determine the optimal dosing regimen during dofetilide treatment51.

Wearable and mobile ECG technologies

AI algorithms can be applied to wearable technologies, enabling rapid, point-of-care diagnoses for patients and consumers. Although many algorithms have been derived using 12-lead ECG data, some studies have demonstrated favourable performance even when algorithms are deployed on single-lead ECGs8. The performance of AI–ECG algorithms for the detection of HCM or the determination of serum potassium levels when applied to single-lead ECGs has been shown not to be significantly different from the performance when applied to 12-lead ECGs45,52.

An international consortium is currently evaluating the ECG as a potential means to diagnose COVID-19, cardiac involvement or the risk of cardiac deterioration, given the known ECG changes and cardiac involvement in patients with COVID-19 (53,54). Although results are not yet available, these types of investigation emphasize the potential power of digitally delivered AI technologies for timely deployment at the point of care and large-scale implementation.

Implementation of AI–ECG

In contrast to data obtained through the clinical history, medical record review or imaging tests, the ease and consistency with which ECG data can be obtained and analysed for the development and implementation of AI models are likely to accelerate the uptake of the AI–ECG in clinical applications, with ensuing increases in workflow efficiency. The preliminary data on the performance of the AI–ECG algorithms are clearly promising, but these technologies will be meaningful only inasmuch as they improve our clinical practice and patient outcomes55.

The algorithm to identify LV dysfunction using the ECG is currently being evaluated in a large-scale, pragmatic, cluster randomized clinical trial56. The EAGLE trial57 randomly assigned >100 clinical teams (or clusters) either to have access to the new AI screening tool results or to usual care at nearly 50 primary care practices (which will encompass >400 clinicians and >24,000 patients) in the Mayo Clinic Health System. Eligible patients include adults who undergo ECG for any reason and in whom low LVEF has not been previously diagnosed. The primary outcome is the detection of low LVEF (<50%), as determined by standard echocardiography. The objective of this study is twofold: to evaluate the real-world efficacy of the algorithm in identifying patients with asymptomatic or previously unrecognized LV dysfunction in primary care practices and to understand how information derived from AI algorithms is interpreted and acted on by clinicians — how do humans and machines interact? This study will validate (or refute) the utility of this approach and will help us to understand potential barriers and opportunities for the implementation of AI in clinical practice. Regardless of its results, the EAGLE trial57 will be an important study because it will be the prototype study for the implementation of AI-enabled tools.

Similarly, we are developing a protocol to assess the algorithm to identify concomitant silent AF or the risk of near-term AF using a 12-lead ECG obtained during normal sinus rhythm. The BEAGLE trial58 will seek to evaluate the utility of this AI algorithm for targeted AF screening in patients who would have at least a moderate risk of stroke if they had AF.

Another application of this algorithm might be in guiding treatment decisions for patients with ESUS. We postulate that these patients might benefit from intensified screening or even empirical anticoagulation on the basis of a high probability of AF, as indicated by the AI–ECG algorithm. Several studies have shown no benefit of empirical anticoagulation in patients with ESUS27,28, but the AI–ECG might help to identify a subset of patients with ESUS in whom recurrent strokes can be prevented.

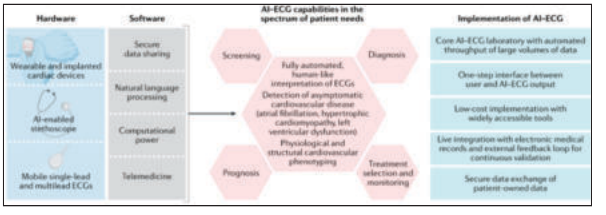


Fig. 3: Framework for AI–ECG applications in clinical practice.

Current, versatile electrocardiogram (ECG)-recording technologies (wearable and implantable devices, smartwatches and e-stethoscopes) coupled with the ability to store, transfer, process and analyse large amounts of digital data are increasingly allowing the deployment of artificial intelligence (AI)-powered tools in the clinical arena, addressing the spectrum of patient needs. The science of AI-enhanced ECG (AI–ECG) implementation, including the interface between patients and the AI–ECG output, integration of AI–ECG tools with electronic health records, patient privacy, and cost and reimbursement implications, is in its infancy and continues to evolve.

Potential challenges and solutions

The AI–ECG technologies offer great promise, but it is important to acknowledge several potential challenges. Given that models are often derived from high-quality databases with meticulously obtained ECGs and well-phenotyped patients, their application to ECGs obtained in routine clinical practice in real-world settings might be poor. Similarly, although the models might perform well in one population, they require rigorous evaluation for external validity in diverse populations. The afore mentioned AI–ECG model for low LVEF has been validated in racially diverse cohorts, but validation data for the other AI–ECG model algorithms are pending. Although models might perform well in terms of their individual performance characteristics, this performance does not always translate into meaningful and actionable clinical information. For instance, screening tests for very rare conditions might be limited by low positive predictive value when applied to populations with low pretest probability of the disease. Although an algorithm might seem to predict a disease state well, if this information does not add to other readily available data (such as age, sex and co morbidities), the algorithm will add very little to clinical risk stratification. Many routinely used screening and diagnostic tests often do not produce consistent improvements in downstream patient outcomes, thereby offering little incremental value to clinical care61. Similar assessments of the effects of routinely integrating the AI–ECG into clinical practice and its implications for patient outcomes and costs will be important. Clearly, the delivery of AI-related applications in the clinical environment generates a new set of previously unrecognized challenges.

As with most other AI-enabled tools, the development of AI–ECG models requires large datasets for training, validation and testing. In some cases, multicentre collaborations might be necessary to assemble the sample sizes required for the development of high-fidelity models. Such collaboration is particularly pertinent when the condition of interest is rare or when an urgent clinical need dictates the rapid development of a model, such as the AI–ECG tools for the diagnosis and risk stratification of COVID-19 during the current pandemic. In this process and during external validation of any AI–ECG model, large amounts of patient data are exchanged between research teams worldwide, generating concerns for the security and protection of sensitive patient information that might be susceptible to cyberattacks or other threats62. In the current environment, the use of traditional encryption methods might not be sufficient to alleviate these concerns. Among other possible novel data-protection solutions, blockchain technology might allow the secure and traceable sharing of patient data between investigators and institutions for the development, validation and clinical implementation of AI tools by generating a decentralized marketplace of securely stored patient data specifically intended to be used in AI applications63,64. Of note, even a miniscule artificial perturbation of the input data (such as a single pixel in an image or an ECG) that is unrecognizable by the human eye might lead an otherwise well-trained CNN to misclassify the data and generate false output. CNNs are clearly vulnerable to adversarial perturbations of input data, and shielding against these vulnerabilities will be important for their future widespread implementation65.

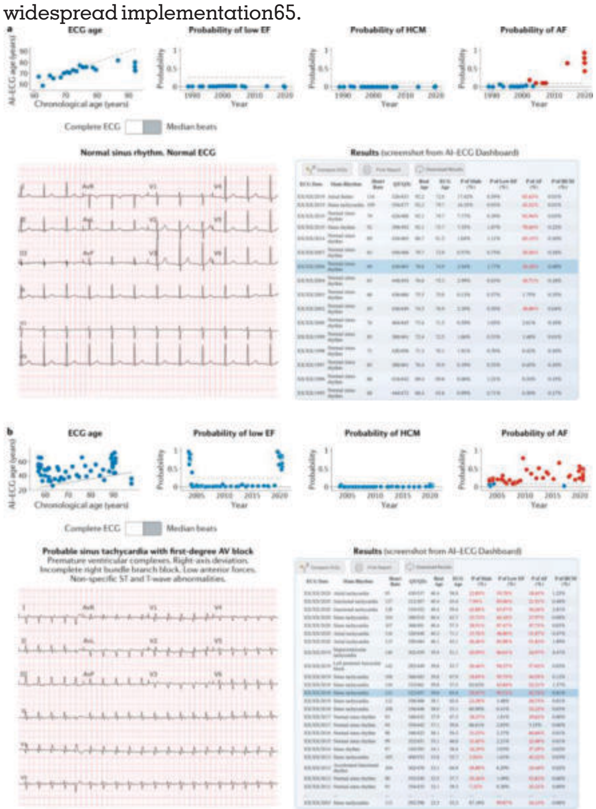


Fig. 4: AI–ECG Dashboard linked from within the electronic health record for point-of-care application.

CONCLUSIONS

Cardiac amyloidosis results in electrocardiographic changes that may develop well ahead of clinical diagnosis and are detected by the application of AI to the standard ECG, a ubiquitous and inexpensive test. The implementation of the AI–ECG is still in its infancy, but a continuously growing clinical investigation agenda will determine the added value of these AI tools, their optimal deployment in the clinical arena and their multifaceted and so-far largely unpredictable implications. Despite increased awareness and improved imaging techniques, delays in diagnosis of CA continue to lead to tragic outcomes. The use of this AI-ECG model to detect CA may promote early diagnosis and initiation of potentially lifesaving therapy.

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