JAMA Cardiology | Original Investigation | AI IN CARDIOLOGY

Detecting Transthyretin Cardiac Amyloidosis With Artificial Intelligence
A Nonrandomized Clinical Trial

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IMPORTANCE Transthyretin amyloid cardiomyopathy (ATTR-CM) is underdiagnosed despite expanding treatment options.

OBJECTIVE To develop and evaluate an artificial intelligence (AI)–augmented clinical program for ATTR-CM detection.

DESIGN, SETTING, AND PARTICIPANTS This nonrandomized clinical trial involved constructing an AI model, ATTRACTnet, using electrocardiogram waveforms, echocardiographic measurements, demographics, and diagnosis codes for orthopedic manifestations of amyloidosis. A single-system, multisite, single-arm, open-label trial was conducted to evaluate its real-world performance. The model was trained and validated at a large academic referral site for ATTR-CM with external validation at an academic site. The trial was conducted as a single-system, multisite trial. Patients with left ventricular (LV) wall thickness 12 mm or more and an ATTRACTnet score 0.5 or higher were eligible. Exclusions included prior ATTR-CM testing, hypertrophic cardiomyopathy, expected life span less than 1 year, nursing home residence, advanced dementia, or LV wall thickness less than 14 mm explained by uncontrolled hypertension or moderate/severe aortic stenosis.

INTERVENTION Eligible patients were notified and offered nuclear scintigraphy testing, monoclonal protein testing, and follow-up care on agreement from the treating physician.

MAIN OUTCOMES AND MEASURE The primary outcome was a diagnosis of ATTR-CM by consensus criteria. ATTR-CM testing positivity was compared with historical and contemporary controls.

RESULTS ATTRACTnet was developed in an internal test set of 799 patients (mean [SD] age, 75.1 [11.1] years; 516 [64.7%] male and 283 [35.3%] female) using 5-fold cross-validation with an additional external test set of 422 patients. It had good discrimination for ATTR-CM detection with an area under the receiver operator characteristic curve of 0.85 (5-fold cross-validation, 0.77-0.85) in the internal set and 0.82 (95% CI, .81-0.83) in the external test set with similar performance in Hispanic, non-Hispanic Black, and non-Hispanic White patients. A total of 1471 patients were identified with positive AI model scores 0.5 or more during the study period, with 256 eligible patients who met study criteria. Of these patients, 50 underwent amyloidosis testing after physician and patient approval; 24 (48%) were diagnosed with ATTR-CM, and 21 (88%) initiated treatment within 3 months. The positivity rate was more than 2.8 times higher than historical controls (15.3%; 95% CI, 13.1%-17.9%; $P < .001$), with an 18% relative increase in new diagnoses vs the prior year.

CONCLUSIONS AND RELEVANCE AI-augmented screening may improve ATTR-CM detection and identify patients who are missed by usual care. Prospective randomized trials are needed to determine if outcomes are improved.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT06469372

Editor's Note

Supplemental content

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JAMA Cardiol. doi:10.1001/jamacardio.2025.4591
Published online November 10, 2025.

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, infiltrative cardiomyopathy caused by abnormal cardiac deposition of misfolded transthyretin (TTR), a protein produced primarily by the liver. ATTR-CM is increasingly recognized as a common cause of heart failure.[1-3] In the United States, ATTR-CM disproportionately affects Black and Hispanic patients, partially driven by a population-specific 3% to 4% prevalence of the isoleucine-for-valine substitution at position 142 (p.Val142Ile) mutation in the *TTR* gene, resulting in TTR tetramer instability and amyloid fibril deposition.[4-15] The initial signs and symptoms of ATTR-CM are nonspecific, leading to underdiagnosis of early-stage ATTR-CM.[16,17] This is particularly true in Black patients, who are often diagnosed with more advanced phenotypes and experience worse outcomes than patients of other races and ethnicities.[7,8]

ATTR-CM is historically associated with high morbidity and mortality, with a median survival of 3.5 years after diagnosis in the absence of treatment.[18] However, treatment options for ATTR-CM are rapidly expanding, with currently approved treatments largely stabilizing rather than reversing cardiac pathology.[19,20] As a result, early diagnosis of ATTR-CM is crucial to delay disease progression and improve outcomes.[1,19,20]

While traditional risk scores and artificial intelligence (AI) models to detect ATTR-CM have been built previously, none of these prior works have prospectively assessed the impact of AI-augmented diagnostic processes on improving the detection of ATTR-CM in real-world settings.[21-23] Therefore, the aims of this study were to (1) develop and externally validate an AI model (ATTRACTnet) to assess if there is benefit above what is achieved by using a validated risk stratification method (ATTR-CM score) and (2) prospectively evaluate an AI-augmented workflow for ATTR-CM screening to assess the impact of identifying undiagnosed ATTR-CM in a diverse population (Cardiac Amyloidosis Discovery Trial) (see 2 recent versions of the trial protocols in Supplement 1 and Supplement 2).

Key Points

Question How well does an artificial intelligence (AI)–augmented screening program detect transthyretin cardiac amyloidosis (ATTR-CM)?

Findings In this nonrandomized clinical trial conducted at multiple sites in a large health system, an AI model identified 1471 patients as positive for potential ATTR-CM, with 256 patients meeting study criteria and eligible for trial inclusion. On physician notification, 50 patients underwent further diagnostic testing, and ATTR-CM was diagnosed in 24 (48%), with treatment initiated in 21 patients (88%).

Meaning AI-augmented clinical programs may identify undiagnosed ATTR-CM and reduce diagnostic delays, but prospective randomized trials are needed to determine if outcomes are improved.

Methods

The Cardiac Amyloidosis Discovery Trial was the open-label, single-arm trial, designed to test AI-augmented detection of undiagnosed ATTR-CM; it was conducted across multiple sites. This study was approved by the Columbia University institutional research board (AAAT2010, AAAU1701) with ClinicalTrials.gov registration (NCT06469372). Patients provided informed consent on enrollment.

ML Model Development and Evaluation for Incremental Benefit in Comparison With ATTR-CM Risk Score Alone (Aim 1)

We identified all patients from 2010 to 2023 at New York-Presbyterian Hospital (NYP) and Columbia University Irving Medical Center who had an electrocardiogram (ECG) and transthoracic echocardiogram (TTE) within 2 years before or 1 year after amyloidosis scintigraphy using either 99mTc-pyrophosphate (PYP) or 99mTc-hydroxymethylene diphosphonate (HMDP) scintigraphy, the most commonly used, guideline-based, noninvasive imaging modality for ATTR-CM (eTable 1 in Supplement 3).[24,25] For the purposes of this study, the scan result was used as the label for ATTR-CM, with a positive test being considered diagnostic for ATTR-CM, while a negative result ruled out ATTR-CM for the training dataset. We extracted tabular features such as patient age, sex, ventricular rate, and ECG intervals such as the QRS duration from the MUSE ECG system (GE Healthcare). The ECG waveforms were abstracted and downsampled for all 12 leads to 250 Hz for a total of 30 000 data points per ECG (12 leads × 10 seconds × 250 Hz). ECGs with ventricular pacing or artifact preventing machine or physician interpretation were excluded (<2% of ECGs). Echocardiographic data were abstracted from TTE reports using Syngo Dynamics (Siemens Healthineers), which included interventricular septal thickness, left ventricular posterior wall thickness (LVPWT), LV end-diastolic dimension, and LV ejection fraction. TTEs had to have all the above measurements to be included. Codes from the *International Classification of Diseases, Ninth Revision,* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* for carpal tunnel syndrome, degenerative joint disease, and lumbar spinal stenosis were used to identify the presence of these diseases documented within the past 2 years from the electronic health record and disease presence or absence was included as tabular data. Race and ethnicity data were obtained from multiple clinical systems and combined into a single race and ethnicity assignment using the following classification: Hispanic, non-Hispanic Black, non-Hispanic White, and other or unknown.[26,27]

Statistical Analysis

An AI model, ATTRACTnet, was constructed with analysis of the ECG waveform using serial residual blocks with a fusion of tabular data, including demographics, TTE measurements, and presence of carpal tunnel syndrome, degenerative joint disease, or lumbar spinal stenosis at the end of the model in the fully connected layer to yield a prediction of whether a patient had ATTR-CM. Performance was assessed

using 5-fold cross-validation for the area under the receiver operator characteristic curve (AUROC) and area under the precision-recall curve with determination of sensitivity, specificity, positive predictive value, and negative predictive value. Patients were stratified to be included in only the train, validation, or test set to maintain strict separation of data and prevent data leakage. Multiple ECG-echo pairs per single patient were allowed in the training dataset for ATTRACTnet as long as the examinations occurred 2 years prior to or 1 year after amyloid scintigraphy. Model performance was evaluated using both all eligible ECG-echo pairs per patient as well as a single pair per patient. When a single pair per patient was used, it consisted of the echocardiogram closest in time to the PYP scan, and the latest ECG by date before that echocardiogram. Further information is provided in the eMethods in Supplement 3. Model accuracy was also separately computed for Hispanic, non-Hispanic Black, and non-Hispanic White patients. Model performance was further assessed in an outside dataset of patients who underwent amyloid scintigraphy at NYP/Weill Cornell Medical Center (WCMC) from 2014 to 2023 who had an ECG and TTE between 2 years before amyloid scintigraphy and 1 year after amyloid scintigraphy. To support further research, a repository related to the model is available on GitHub.[28]

Prospective Evaluation of AI-Augmented Screening for ATTR-CM (Aim 2)

We conducted the Cardiac Amyloidosis Discovery Trial, an open-label, single-arm trial designed to test AI-augmented detection of undiagnosed ATTR-CM across multiple sites. Patients 50 years and older with an ECG and TTE within 2 years with LV wall thickness 12 mm or greater (or ≥14 mm in the setting of uncontrolled hypertension or moderate or severe aortic stenosis) who had an AI model score of at least 0.5 were eligible for inclusion. Exclusion criteria included prior ATTR-CM testing, nursing facility residence, dementia, expected life span less than 1 year, or a diagnosis of hypertrophic cardiomyopathy. These study criteria were chosen to ensure that a diagnosis of ATTR-CM could be made noninvasively according to multisociety guidelines,[24] acknowledging that aortic stenosis and hypertension can coexist with cardiac amyloidosis. Patients who had no mention of suspected cardiac amyloidosis in clinical notes and no orders for amyloidosis testing were considered for enrollment. As part of this study, echocardiograms were re-reviewed by study investigators to ensure that patients met study criteria. Patients with wall thickness on remeasurement that did not meet criteria were excluded from the study. The study was planned to enroll up to 100 patients with interim analyses to guide future deployment efforts.

The treating primary care physician or cardiologist for patients identified by the model was contacted for approval (eFigure 1 in Supplement 3). Clinicians were contacted through in-basket and direct messaging through the electronic health record. Follow-up messages were sent to clinicians who did not respond within 1 week. Once approved, eligible patients were offered 99mTc-PYP or 99mTc-HMDP cardiac amyloidosis scintigraphy and monoclonal protein testing either in the Columbia research setting or local clinical settings at the discretion of the treating clinician (eFigure 2 in Supplement 3). Testing in the Columbia research setting was paid for by study funds and interpreted by study investigators. Local clinical testing was billed to insurance and interpreted by local cardiologists with confirmation of results by study investigators.

Statistical Analysis

The primary outcome was an ATTR-CM diagnosis determined by consensus criteria.[26,27] Every patient with possible cardiac uptake on planar imaging underwent single-photon emission computed tomography (SPECT) imaging to evaluate for myocardial uptake. The presence or absence of myocardial uptake on SPECT imaging was used as diagnostic criteria for ATTR-CM. The percentage of patients diagnosed with ATTR-CM in the study population was compared with that of historical and contemporary controls using χ^2 testing. Confidence intervals for the positive predictive value in the trial population and control arms were determined using Wilson binomial 95% confidence intervals. Historical controls include all patients evaluated by amyloid scintigraphy across the same sites for ATTR-CM in the 12 months preceding the start of the trial from May 2023 to May 2024 (n = 887), while contemporary controls include all patients evaluated by amyloid scintigraphy through routine clinical care during the same time period as the trial from May 2024 to May 2025 (n = 854).

In addition to the primary analysis using a historical control population of all patients who underwent amyloid scintigraphy, we also identified a subset of those historical and contemporary control patients who met the same criteria as those recruited in the trial, including a TTE in our system within prior 2 years meeting LV wall thickness criteria. The rate of cardiac amyloid scintigraphy positivity in this subset was compared with the trial population in an exploratory analysis. We report our findings using a confusion matrix, and report sensitivity, specificity, positive predictive value, and negative predictive value. Statistical analysis was performed in Stata version 17.0 (StataCorps) and Python version 3.70 (Python Software Foundation).

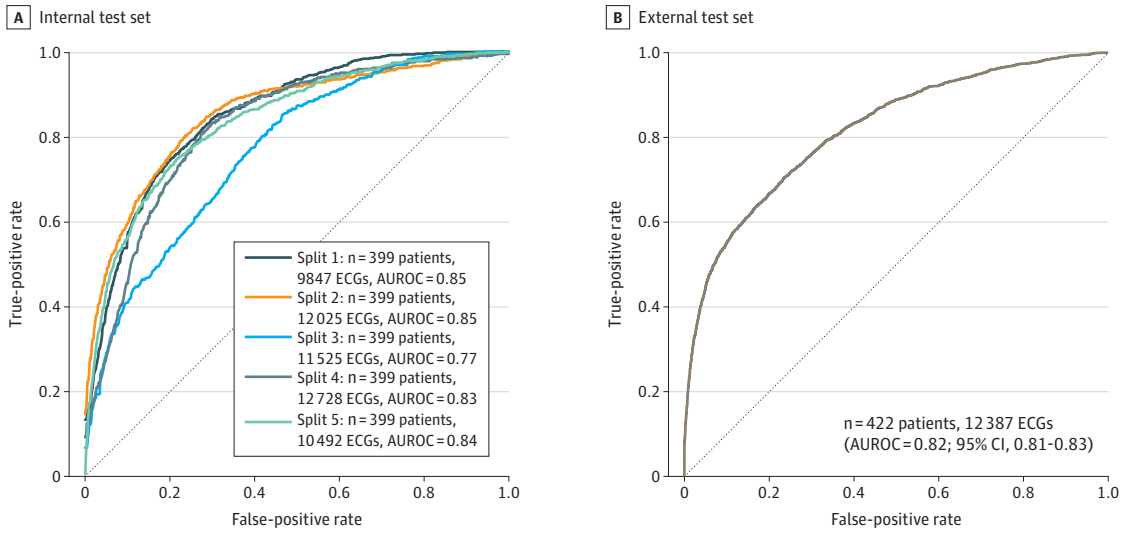
The investigators conducted interim analyses throughout the study period, consistent with its pilot design. This included formal statistical analyses at recruitment of 25 and 50 patients. In light of (1) the high positivity rate of patients recruited into the trial, (2) the substantial difference between positivity rates in the trial and control populations, (3) and unlikelihood that recruitment to 100 patients would meaningfully affect the study results, particularly in the context of the limitations of its single-arm design, the decision was made to report these interim results.

Results

Derivation, Validation, and Testing of ATTRACTnet and Assessment of Benefit in Excess of Other Risk Stratification (Aim 1)

To develop and test ATTRACTnet, we included 799 patients with 22 344 ECG and TTE pairings completed within 2 years of amyloid scintigraphy between 2010-2023 (eFigure 3A in

Figure 1. Area Under the Receiver Operator Characteristic Curve (AUROC) Curves for Artificial Intelligence Model



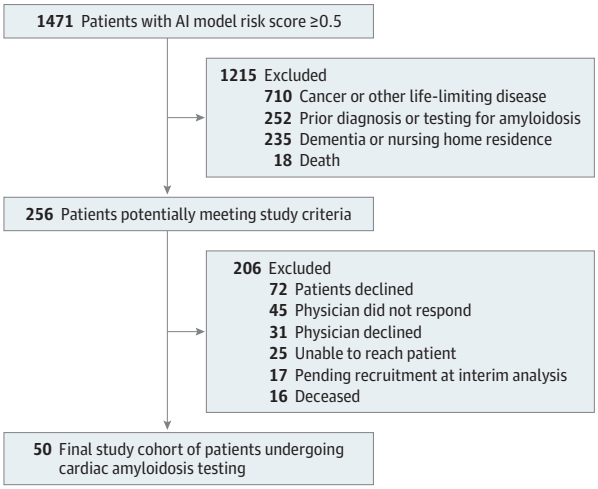
AUROC curves for the 5 folds used during validation (A) and the AUROC curve for the external test set (B).

Supplement 3). The mean (SD) age was 75.1 (11.1) years; 516 (64.7%) were male and 283 (35.3%) were female. Amyloid scintigraphy was positive for ATTR-CM in 12.8% of ECG-TTE pairs and 20.7% of patients. Using 5-fold cross-validation, the dataset was shuffled and split into 5 training/testing splits. The external test set from NYP/WCMC included 422 patients with 12 387 ECG-TTE pairs (17.0% of ECG-TTE pairs and 22.7% of patients positive for ATTR-CM) (eFigure 3B in Supplement 3).

Demographic and clinical characteristics for ECG-TTE pairs in the test/validation and external validation cohorts are summarized in eTable 2 in Supplement 3. Per-patient characteristics for the test/validation cohort are detailed in eTable 3 in Supplement 3. Model accuracy for 5-fold cross-validation and external test set is shown in **Figure 1**. We proceeded with split 2 model weights for external testing. The model cutpoint was selected to maximize positive predictive value to facilitate efficient opportunistic testing in the subsequent trial given the cost and radiation exposure of ATTR-CM testing. At a threshold of 0.5, performance metrics evaluated using the latest ECG per patient in the internal holdout set were as follows: sensitivity of 0.56, specificity of 0.92, negative predictive value of 0.84, and positive predictive value of 0.74. The difference in AUROC between each racial and ethnic subgroup was compared (eTable 4 in Supplement 3) and showed no evidence of difference between groups. The model had an AUROC of 0.82 (95% CI, 0.81-0.83) in the external test set (Figure 1), and performance metrics are detailed in eFigure 4 in Supplement 3.

To understand how many patients across the system could have elevated risk for ATTR-CM and how this list could be narrowed by an AI assessment, we applied the ATTR-CM[21] score to the 93 570 patients from 2010 to 2023 who did not have amyloid scintigraphy but did have an ECG and TTE, of whom 14 585 (15.6%) were older than 50 years with LVPWT of at least 12 mm. Of this subgroup, the ATTR-CM score identified 9892 patients (67.8%) as having elevated risk for ATTR-CM, acknowledging that not all of these patients would have clinical diagnoses of heart failure. In the same time frame, only 1515 patients were tested for ATTR-CM in routine clinical care. Of those 9892 patients at elevated risk by ATTR-CM score, 1196 (12.1%) had an ATTRACTnet score of 0.5 or more.

Figure 2. Cardiac Amyloidosis Discovery Trial Flow Diagram



AI indicates artificial intelligence.

Cardiac Amyloidosis Discovery Initial Trial Results (Aim 2)

From May 2024 to May 2025, 256 patients 50 years and older met eligibility criteria (**Figure 2**). The physicians of these patients were contacted: for 180 patients (70.3%), testing was physician approved; for 45 (17.6%), there was no physician response; and for 31 (12.1%), the physician declined to test. Of these 180 physician-approved patients, 72 patients (40.0%) declined testing, 25 (13.9%) were unable to be reached, and 16

Table. Patient Characteristics at 8 Sites From 2023 to 2025

	Trial population, No. (%)			Historical controls, No. (%)			Contemporary controls, No. (%)		
	ATTR-CM positive (n = 24)	ATTR-CM negative (n = 26)	Total (n = 50)	ATTR-CM positive (n = 136)	ATTR-CM negative (n = 751)	Total (n = 887)	ATTR-CM positive (n = 145)	ATTR-CM negative (n = 709)	Total (n = 854)
Age, mean (SD), y	85 (7)	76 (10)	80 (10)	82 (9)	74 (12)	75 (12)	79 (9)	74 (11)	75 (11)
Sex									
Male	15 (62)	17 (65)	32 (64)	95 (70)	427 (57)	522 (59)	100 (69)	375 (53)	475 (56)
Female	9 (38)	9 (35)	18 (36)	41 (30)	324 (43)	365 (41)	45 (31)	334 (47)	379 (44)
Race and ethnicity[a]									
Hispanic	4 (17)	6 (23)	10 (20)	13 (10)	93 (12)	106 (12)	9 (6)	80 (11)	89 (10)
Non-Hispanic Black	8 (33)	6 (23)	22 (44)	42 (31)	254 (34)	296 (33)	54 (37)	269 (38)	323 (38)
Non-Hispanic White	10 (42)	6 (23)	16 (32)	57 (42)	287 (38)	344 (39)	57 (39)	256 (36)	313 (37)
Other or unknown	2 (8)	0	2 (4)	24 (18)	117 (16)	141 (16)	25 (17)	104 (15)	129 (15)
Patients with a TTE	24 (100)	26 (100)	50 (100)	108 (79)	652 (87)	760 (86)	122 (84)	623 (88)	745 (87)
Maximum LV wall thickness, mean (SD), mm	17 (2)	17 (3)	17 (3)	16 (4)	13 (3)	14 (3)	16 (4)	13 (3)	14 (4)
LVEDD, mean (SD), mm	43 (7)	46 (8)	45 (7)	46 (7)	50 (8)	50 (8)	46 (7)	50 (8)	49 (8)
LVEF, mean (SD), %	56 (10)	60 (9)	58 (10)	53 (13)	56 (13)	55 (13)	54 (13)	56 (13)	55 (13)
Patients with an ECG	24 (100)	26 (100)	50 (100)	123 (90)	622 (83)	745 (84)	127 (88)	597 (84)	724 (85)
LVH	6 (25)	15 (58)	21 (42)	44 (36)	256 (41)	300 (40)	48 (38)	276 (46)	324 (45)
Low voltage	6 (25)	2 (8)	8 (16)	25 (20)	86 (14)	111 (15)	20 (16)	82 (14)	102 (14)
Orthopedic manifestations									
Carpal tunnel syndrome	4 (17)	3 (12)	7 (14)	26 (19)	51 (7)	77 (9)	23 (16)	56 (8)	79 (9)
Degenerative joint disease	4 (17)	2 (8)	6 (12)	15 (11)	72 (10)	87 (10)	5 (3)	58 (8)	63 (7)
Spinal stenosis	5 (21)	2 (8)	7 (14)	14 (10)	59 (8)	73 (8)	9 (6)	61 (9)	70 (8)

Abbreviations: ATTR-CM, transthyretin cardiac amyloidosis; ECG, electrocardiogram; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVH, LV hypertrophy; TTE, transthoracic echocardiogram.

[a] Race and ethnicity data were obtained from multiple clinical systems and combined into a single race and ethnicity assignment using Hispanic, non-Hispanic Black, non-Hispanic White, and other or unknown.

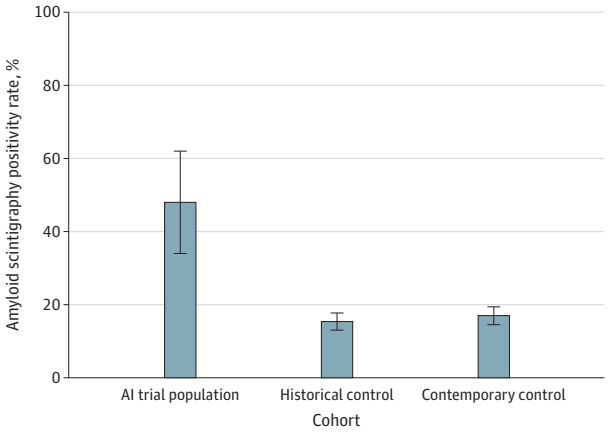
(8.9%) patients died before outreach and scheduling of ATTR-CM testing, yielding 67 patients (37.2%). At the time of analysis, 50 patients had undergone cardiac amyloid testing (19 in the Columbia research setting and 31 in local clinical settings) (eFigure 5 in Supplement 3). A total of 24 patients (48.0%; 95% CI, 34.8%-61.5%) tested positive for ATTR-CM. A single patient in a local setting did not undergo monoclonal protein testing after shared decision-making regarding treatment options; the remainder were not found to have AL-CM (**Table** and **Figure 3**). All patients diagnosed with ATTR-CM received referrals to heart failure specialists, and 21 of the diagnosed patients (88%) were prescribed ATTR-CM therapy within 3 months of diagnosis.

The performance of the AI-augmented clinical program was significantly higher than routine clinical care in the prior 12 months (historical control), during which time the percentage of positive diagnoses within all PYP scans conducted was 15.3% (95% CI, 13.1%-17.9%; $P < .001$). The trial positivity rate was also significantly higher than that observed in the contemporary control population who underwent testing between May 2024 and May 2025 (17.0%; 95% CI, 14.6%-19.6%; $P < .001$) (Table). There was no significant difference between the rate of positive tests in the historical and contemporary control groups.

We assessed when ATTRACTnet would have identified patients as high risk based on evaluating all older ECGs and TTEs. When the algorithm was applied to all prior ECGs and TTEs meeting trial criteria, patients who were diagnosed with ATTR-CM through the trial had their first positive risk score a median of 345 days (IQR, 891 days) before study enrollment. Combined rates of diagnosis in Hispanic and non-Hispanic Black patients were numerically higher than historical and contemporary controls, with 12 of positive patients (50.0%) in the trial being from 1 of these 2 groups, compared with 55 (40.4%) of the positive patients in the historical control.

In the historic control population, we identified a subset of 449 patients who met the same LV wall thickness inclusion criteria as the intervention population (of the 887 original historic controls). Of these patients, 89 (19.8%) were found to have ATTR-CM compared with 136 (15.3%) of the entire historic control population. In the contemporary control population, we identified 480 patients who met these criteria (of the 854 original contemporary controls). Of these patients, 102 (21.3%) were found to have ATTR-CM compared with 145 (17.0%) of the entire contemporary control population. These positivity rates remained significantly lower than patients enrolled in the trial (24/50 [48%]; $P < .001$). The sensitivity of the model in pa-

Figure 3. Cardiac Amyloidosis Discovery Trial Results



The artificial intelligence–augmented program yielded a 48% positivity rate (95% CI, 34.8%-61.5%). This rate of positive transthyretin cardiac amyloidosis diagnoses among patients referred for nuclear scintigraphy using ATTRACTnet was more than 2.8 times higher than both historical controls (15.3%; 95% CI, 13.1%-17.9%; $P < .001$) and contemporary controls (17.0%; 95% CI, 14.6%-19.6%; $P < .001$).

tients who underwent amyloid scintigraphy was 0.72 and specificity was 0.78 (eFigure 6 in Supplement 3).

Discussion

Using contemporary data at a large, urban referral center for ATTR-CM serving a diverse population, we developed, validated, and prospectively deployed an AI model, ATTRACTnet, to augment the detection of ATTR-CM. In a single-arm, single-system, multisite clinical trial, ATTRACTnet successfully identified high-risk patients not previously diagnosed by routine care. This system was prospectively found to detect ATTR-CM in 48% of the tested population, of whom 88% were prescribed ATTR-CM therapy within 3 months of diagnosis. Among those tested, the positivity rate was more than 2.8 times higher than historical controls, resulting in an 18% relative increase in systemwide diagnoses compared with the previous year.

Machine learning models have been previously developed to augment the diagnostic process for ATTR-CM. Huda et al[22] used medical claims data to develop a random forest ML model to predict wild-type ATTR-CM, and many groups have successfully developed ECG and TTE models to predict cardiac amyloidosis.[29-35] However, these studies have not undergone prospective deployment and evaluation of AI-augmented workflows.

Given limitations in current risk scoring models, more specific tools are needed to identify high-risk patients with a sufficient positive predictive value to warrant ATTR-CM testing. In our population, the ATTR-CM score identified 9892 patients as potentially at risk for cardiac amyloidosis, underscoring the practical challenges of implementing existing risk scores within capacity-constrained clinical settings. Of those 9892 patients, 1196 (12.1%) had an ATTRACTnet score of 0.5 or more, suggesting that this algorithm could be useful in identifying patients most likely to benefit from testing. To support widespread use of this model and serve as an accelerant for future research, we are making available code related to development for public use.

The open-label, single-arm trial assessed if our AI-augmented workflow could allow for improved identification of undetected ATTR-CM. The detection program to identify undiagnosed ATTR-CM successfully found patients with an ATTR-CM diagnosis at a rate significantly higher than historical and contemporary controls. Importantly, identified patients were not otherwise being considered for ATTR-CM within current clinical care, and if the algorithm had been in effect, these patients could have been identified an average of 345 days sooner. Of patients diagnosed, 88% went on to start ATTR-CM treatment within 3 months of diagnosis. Finally, this program was effective in identifying ATTR-CM in Hispanic and non-Hispanic Black patients.

AI models have had widespread success in disease discrimination in retrospective datasets, but there have been limited rigorous studies of their utility to improve disease diagnosis. The challenges of deployment of AI models into clinical care include (1) a lower prevalence of disease in unselected populations, (2) the creation of systems capable of delivering close to real-time, actionable AI results, and (3) staffing requirements for clinical outreach. The challenges of AI model deployment are largely not about the AI technology itself, but rather around implementing new systems and programs into routine clinical care.

It is important to note that only 50 patients ultimately underwent amyloid scintigraphy, in large part because of real-world challenges in implementation. Of the 256 patients who met full study criteria, many did not proceed to testing because their physicians did not respond to outreach, or the patients themselves declined or could not be contacted. These operational drop-offs reflect barriers in deploying novel screening tools within clinical practice. The diagnostic yield of 48% among those tested illustrates the model's capacity to identify true cases, even when applied in a pilot study. Given the success in this pilot study with high diagnostic yield over historical controls while accounting for the limitations of this uncontrolled trial, the decision was made to report these findings to both highlight challenges with clinical AI deployment and support the design of a definitive controlled study.

Limitations

This study should be interpreted within the context of several limitations. First, ATTR-CM has historically been underdiagnosed, which can challenge the development of ML models given small training datasets. This current study assembled one of the largest datasets, which improves model accuracy, but larger datasets would likely improve model performance. Of note, there was a drop in specificity in the historical external test set. It is possible this was caused by including scintigraphy data from the earliest years of testing, when practice patterns may have significantly differed, but it is unclear. This drop in specificity was not seen in prospective cohorts at the same external site or any of the 6 other external sites not included in training. Second, our

trial was performed in a single 8-hospital system, which may limit generalizability, and was a single-arm design with a relatively small number of enrolled patients. However, none of the patients enrolled in the study had been suspected of cardiac amyloidosis, which suggests the value of AI-augmented clinical pathways for this disease. Third, in the prospective trial, we selected a model threshold that prioritized specificity and positive predictive value, given the importance of building clinician and patient trust and the need to manage resource-intensive testing. This choice yielded a sensitivity of 0.56, which we acknowledge limits the ability to capture all possible cases. Our goal was to help increase identification of missed cases, not to replace current diagnostic approaches for ATTR-CM. Future studies will be needed to confirm efficacy across broader populations. Fourth, the high rate of positivity was in part due to the enriched nature of the study population, where all patients tested had increased LV wall thickness. When these same restriction criteria were applied to the historic and contemporary controls, the trial population rate of positivity was 2.4 times and 2.2 times higher, respectively, compared with 2.8 times higher without restriction.

Conclusions

An AI-augmented diagnostic program using ATTRACTnet, a machine learning model, may lead to additional ATTR-CM diagnoses. By integrating the model into clinical workflows across multiple sites, we identified high-risk patients who were not previously being evaluated for ATTR-CM. The positive test rate was more than 2.8 compared with historical and contemporary controls, with a meaningful increase in newly diagnosed cases and substantial representation of underdiagnosed racial and ethnic groups. These findings support the potential of AI-driven screening to close critical diagnostic gaps in ATTR-CM and may aid in the design of future real-world testing of the implementation of AI-based diagnostic programs.

ARTICLE INFORMATION

Accepted for Publication: October 17, 2025.

Published Online: November 10, 2025. doi:10.1001/jamacardio.2025.4591

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Obtained funding: Tatonetti, Homma, Poterucha.
Administrative, technical, or material support: Jain, Roedan Oliver, Malta, Castillo, Wan, Alishetti, Brown, Witteles, Goyal, Homma, Maurer, Elias, Poterucha.
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Conflict of Interest Disclosures: Dr Jain reported consulting fees from Bristol Myers Squibb, ARTIS Ventures, and Broadview Ventures outside of the submitted work. Dr Roedan Oliver reported grants from Eidos and grants from Pfizer during the conduct of the study. Dr Malta reported grants from Eidos and Pfizer during the conduct of the study. Ms Castillo reported grants from the American Heart Association, Eidos Therapeutics, Pfizer, and Janssen Pharmaceuticals during the conduct of the study. Dr Tatonetti reported options from CARI Health, Inc, and personal fees from World Quant Foundry outside the submitted work. Dr Rodriguez reported grants from the National Institutes of Health National Heart, Lung, and Blood Institute (R01HL168188, R01HL167974, R01HL169345) and Doris Duke Foundation (2022051) during the conduct of the study and consulting fees from Novartis, Novo Nordisk, Esperion Therapeutics, Movano Health, Kento Health, Edwards, Arrowhead Pharmaceuticals, HeartFlow, iRhythm, Amgen, and Cleerly Health outside the submitted work. Dr Witteles reported personal fees from Pfizer, Alnylam, BridgeBio, Astra Zeneca, and Alexion outside the submitted work. Dr Einstein reported personal fees from Artrya, Axcellant, Canon Medical Systems USA, Ionetix, United States Nuclear Regulatory Commission, W. L. Gore & Associates, and Wolters Kluwer Healthcare—UpToDate and grants from Alexion, Attralus, BridgeBio, Canon Medical Systems USA, GE HealthCare, Intellia Therapeutics, International Atomic Energy Agency, Ionis Pharmaceuticals, National Institutes of Health, Neovasc, Pfizer, Roche Medical Systems, Shockware Medical, and W. L. Gore & Associates outside the submitted work. Dr Maurer reported personal fees from Pfizer, AstraZeneca, and Bayer and grants from Alnylam, Ionis, Attralus, Intellia, BridgeBio Inc, and Novo Nordisk during the conduct of the study and personal fees from Pfizer, Ionis, Alnylam, Intellia, and Novo Nordisk outside the submitted work. Dr Elias reported equity from Pathwai and grants from Pfizer Eidos during the conduct of the study and grants from Edwards Life Sciences and personal fees from GE Healthcare outside the submitted work. Dr Poterucha reported grants from Pfizer and Eidos/BridgeBio during the conduct of the study; grants from Janssen and stock ownership from Baxter Abbott Laboratories outside the submitted work; and having a patent issued for EchoNext-AI ECG for structural heart disease detection. No other disclosures were reported.

Meeting Presentation: This paper was presented at AHA Scientific Sessions 2025; November 10, 2025; New Orleans, Louisiana.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We acknowledge the Dalio Center for Health Justice for their assistance in the curation of racial and ethnicity data used throughout this article.

Additional Information: Artificial intelligence tools were used to aid in the editing of this manuscript for clarity. These tools were used under human oversight, and all scientific content, analysis, and conclusions reflect the authors' original work and judgment. All final content was determined and approved by the authors.

REFERENCES

1. Maurer MS, Schwartz JH, Gundapaneni B, et al; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid

cardiomyopathy. *N Engl J Med*. 2018;379(11):1007-1016. doi:10.1056/NEJMoa1805689

2. Goland S, Volodarsky I, Fabricant Y, et al. Wild-type TTR amyloidosis among patients with unexplained heart failure and systolic LV dysfunction. *PLoS One*. 2021;16(7):e0254104. doi:10.1371/journal.pone.0254104

3. Bhattacharya PT, Teruya SL, De Los Santos J, Helmke S, Maurer MS. Heart failure with reduced ejection fraction: an under-appreciated clinical phenotype of transthyretin cardiac amyloid (ATTR-CA). *J Card Fail*. 2022;28(5)(suppl):S35-S36. doi:10.1016/j.cardfail.2022.03.095

4. Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. *Amyloid*. 2015;22(3):171-174. doi:10.3109/13506129.2015.1051219

5. Jacobson DR, Pastore RD, Yaghoubian R, et al. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in Black Americans. *N Engl J Med*. 1997;336(7):466-473. doi:10.1056/NEJM199702133360703

6. Buck FS, Koss MN, Sherrod AE, Wu A, Takahashi M. Ethnic distribution of amyloidosis: an autopsy study. *Mod Pathol*. 1989;2(4):372-377.

7. Shah KB, Mankad AK, Castano A, et al. Transthyretin cardiac amyloidosis in Black Americans. *Circ Heart Fail*. 2016;9(6):e002558. doi:10.1161/CIRCHEARTFAILURE.115.002558

8. Spencer-Bonilla G, Njoroge JN, Pearson K, Witteles RM, Aras MA, Alexander KM. Racial and ethnic disparities in transthyretin cardiac amyloidosis. *Curr Cardiovasc Risk Rep*. 2021;15(6):8. doi:10.1007/s12170-021-00670-y

9. Quarta CC, Buxbaum JN, Shah AM, et al. The amyloidogenic V122I transthyretin variant in elderly Black Americans. *N Engl J Med*. 2015;372(1):21-29. doi:10.1056/NEJMoa1404852

10. Alexander KM, Orav J, Singh A, et al. Geographic disparities in reported US amyloidosis mortality from 1979 to 2015: potential underdetection of cardiac amyloidosis. *JAMA Cardiol*. 2018;3(9):865-870. doi:10.1001/jamacardio.2018.2093

11. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. *Genet Med*. 2017;19(7):733-742. doi:10.1038/gim.2016.200

12. Leedy DJ, Cuddy SAM, Cheng RK. Transthyretin cardiac amyloidosis: underrecognized in the underrepresented. *J Am Heart Assoc*. 2023;12(15):e030802. doi:10.1161/JAHA.123.030802

13. Madhani A, Sabogal N, Massillon D, et al. Clinical penetrance of the transthyretin V122I variant in older Black patients with heart failure: the SCAN-MP (Screening for Cardiac Amyloidosis With Nuclear Imaging in Minority Populations) study. *J Am Heart Assoc*. 2023;12(15):e028973. doi:10.1161/JAHA.122.028973

14. Chandrashekar P, Alhuneafat L, Mannello M, et al. Prevalence and outcomes of p.Val142Ile TTR amyloidosis cardiomyopathy: a systematic review. *Circ Genom Precis Med*. 2021;14(5):e003356. doi:10.1161/CIRCGEN.121.003356

15. Damrauer SM, Chaudhary K, Cho JH, et al. Association of the V122I hereditary transthyretin amyloidosis genetic variant with heart failure among individuals of African or Hispanic/Latino ancestry. *JAMA*. 2019;322(22):2191-2202. doi:10.1001/jama.2019.17935

16. Rapezzi C, Lorenzini M, Longhi S, et al. Cardiac amyloidosis: the great pretender. *Heart Fail Rev*. 2015;20(2):117-124. doi:10.1007/s10741-015-9480-0

17. Rozenbaum MH, Large S, Bhambri R, et al. Impact of delayed diagnosis and misdiagnosis for patients with transthyretin amyloid cardiomyopathy (ATTR-CM): a targeted literature review. *Cardiol Ther*. 2021;10(1):141-159. doi:10.1007/s40119-021-00219-5

18. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol*. 2016;68(10):1014-1020. doi:10.1016/j.jacc.2016.06.033

19. Rettl R, Mann C, Duca F, et al. Tafamidis treatment delays structural and functional changes of the left ventricle in patients with transthyretin amyloid cardiomyopathy. *Eur Heart J Cardiovasc Imaging*. 2022;23(6):767-780. doi:10.1093/ehjci/jeab226

20. Fontana M, Berk JL, Gillmore JD, et al; HELIOS-B Trial Investigators. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2024;392(1):33-44. doi:10.1056/NEJMoa2409134

21. Davies DR, Redfield MM, Scott CG, et al. A simple score to identify increased risk of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. *JAMA Cardiol*. 2022;7(10):1036-1044. doi:10.1001/jamacardio.2022.1781

22. Huda A, Castaño A, Niyogi A, et al. A machine learning model for identifying patients at risk for wild-type transthyretin amyloid cardiomyopathy. *Nat Commun*. 2021;12(1):2725. doi:10.1038/s41467-021-22876-9

23. Goto S, Mahara K, Beussink-Nelson L, et al. Artificial intelligence-enabled fully automated detection of cardiac amyloidosis using electrocardiograms and echocardiograms. *Nat Commun*. 2021;12(1):2726. doi:10.1038/s41467-021-22877-8

24. Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 1 of 2, evidence base and standardized methods of imaging. *Circ Cardiovasc Imaging*. 2021;14(7):e000029.

25. Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 2 of 2, diagnostic criteria and appropriate utilization. *Circ Cardiovasc Imaging*. 2021;14(7):e000030. doi:10.1161/HCI.0000000000000030

26. Estrada-Veras JI, Cabrera-Peña GA, Pérez-Estrella de Ferrán C. Medical genetics and genomic medicine in the Dominican Republic: challenges and opportunities. *Mol Genet Genomic Med*. 2016;4(3):243-256. doi:10.1002/mgg3.224

27. Montinaro F, Busby GBJ, Pascali VL, Myers S, Hellenthal G, Capelli C. Unravelling the hidden ancestry of American admixed populations. *Nat Commun*. 2015;6(1):6596. doi:10.1038/ncomms7596

28. GitHub. IntroECG: /8-CADNet ATTR Model. Accessed October 24, 2025. https://github.com/PierreElias/IntroECG/tree/master/8-CADNet%20ATTR%20Model

29. Oikonomou EK, Sangha V, Shankar SV, et al. Artificial intelligence-enabled electrocardiography and echocardiography to track preclinical progression of transthyretin amyloid cardiomyopathy. *Eur Heart J*. 2025;46(37):3651-3662. doi:10.1093/eurheartj/ehaf450

30. Grogan M, Lopez-Jimenez F, Guthrie S, et al. Value of artificial intelligence for enhancing suspicion of cardiac amyloidosis using electrocardiography and echocardiography: a narrative review. *J Am Heart Assoc*. 2025;14(8):e036533. doi:10.1161/JAHA.124.036533

31. Grogan M, Lopez-Jimenez F, Cohen-Shelly M, et al. Artificial intelligence-enhanced electrocardiogram for the early detection of cardiac amyloidosis. *Mayo Clin Proc*. 2021;96(11):2768-2778. doi:10.1016/j.mayocp.2021.04.023

32. Duffy G, Cheng PP, Yuan N, et al. High-throughput precision phenotyping of left ventricular hypertrophy with cardiovascular deep learning. *JAMA Cardiol*. 2022;7(4):386-395. doi:10.1001/jamacardio.2021.6059

33. Slivnick JA, Hawkes W, Oliveira J, et al. Cardiac amyloidosis detection from a single echocardiographic video clip: a novel artificial intelligence-based screening tool. *Eur Heart J*. 2025;46(40):4090-4101. doi:10.1093/eurheartj/ehaf387.

34. Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. *Science*. 2019;366(6464):447-453. doi:10.1126/science.aax2342

35. Hourmozdi J, Easton N, Benigeri S, et al. Evaluating the performance and potential bias of predictive models for detection of transthyretin cardiac amyloidosis. *JACC Adv*. 2025;4(8):101901. doi:10.1016/j.jacadv.2025.101901