SUPPLEMENTAL MATERIAL

Supplemental Table 1: Recent machine learning and artificial intelligence studies in clinical cardiac electrophysiology

Authors	Clinical application	Data	Machine learning algorithm	Results
Disease detection and diagnosis				
Li et al[1]	Automated ventricular fibrillation and tachycardia classification	Public domain ECG databases were used for training, validation, and testing: American Heart Association database, Creighton University Ventricular Tachyarrhythmia Database, and the MIT-BIH Malignant Ventricular Arrhythmia Database	Supervised support vector machine	Classified arrhythmia on the out-of-sample validation data with 96% accuracy, 96% sensitivity, and 96% specificity
Acharya et al[2]	Automated classification of heartbeats: non-ectopic, supraventricular ectopic, ventricular ectopic, fusion, and unknown	48 half-hour long Lead II ECG recordings from 47 subjects in the MIT-BIH Arrhythmia database	Supervised deep learning (CNN)	Classified heartbeats with accuracy of 94%
Teijeiro et al[3]	Part of the 2017 PhysioNet/CinC Challenge - Automated classification of Holter ECG: normal, AF, other	Trained using 8183 single-lead ECGs and tested on 3658	Supervised deep learning (RNN) combined with a supervised gradient boosting classifier	Classified ECG with an overall F1 score of 0.83, which ranked first in the PhysioNet/CinC competition

	arrhythmia, or noisy			
Hannun et al[4]	Automated arrhythmia classification	Trained on 91,232 single-lead ECGs from ambulatory ECG monitoring devices on 53,549 patients, and tested on 328 ECGs from 328 unique patients	Supervised deep learning (CNN)	Classified 12 different arrhythmias with an average AUC of 0.97 and an F1 score of 0.84, exceeding that of an average cardiologist (0.78)
Attia et al[5]	Detecting asymptomatic LV dysfunction from ECG	Trained on 12-lead ECGs from 44,959 patients, and tested on 12-lead ECGs of 52,870 patients	Supervised deep learning (CNN)	Detected ventricular dysfunction with an AUC of 0.93. Patients without LV dysfunction but positive ECG screen had 4 times the risk of developing future LV dysfunction.
Galloway et al[6]	Detecting hyperkalemia from ECG	Trained on 1,576,581 ECGs from 449,380 patients, and tested on ECGs of 61,965 patients. Only used 2 or 4 leads.	Supervised deep learning (CNN)	Detected hyperkalemia with an AUC of 0.85-0.90
Attia et al[7]	Atrial fibrillation detection on sinus rhythm ECG	Trained on 454,789 sinus rhythm ECGs from 126,526 patients, and tested on 1380,802 sinus rhythm ECGs from 36,820 patients.	Supervised deep learning (CNN)	A single ECG identified atrial fibrillation with an AUC of 0.87 and F1 score of 0.39. Including multiple ECGs increased the AUC to 0.90 and the F1 score to 0.45.

Tison et al[8]	Atrial fibrillation detection on smartwatch	Trained on 9750 patients with smartwatch photo-plethysmography, and tested on 51 patients undergoing cardioversion	Unsupervised deep learning followed by supervised classification (semi-supervised)	AF detection with an AUC of 0.97 in patients who underwent cardioversion, and an AUC of 0.72 in self-reported ambulatory patients.
Wasserlauf et al[9]	Atrial fibrillation detection on smartwatch	Trained with heart rate, activity level, and ECGs from smartwatches of 7500 subjects, with testing on 24 patients	Supervised deep learning (CNN)	Compared with insertable cardiac monitor, smartwatch detected AF with episode sensitivity of 97.5%, PPV of 39.9%, and duration sensitivity of 97.7%
Bumgarner et al[10]	Atrial fibrillation detection on smartwatch	Kardia Band rhythm strip recording on Apple Watch, evaluated on 100 enrolled patients	Kardia Band algorithm (proprietary)	Compared with ECG, the KB interpreted AF with 93% sensitivity, 84% specificity, and a K coefficient of 0.77
Yan et al[11]	Atrial fibrillation detection on smartphone camera	An ML algorithm using facial and fingertip PPG data obtained from iPhone camera was tested on 217 cardiology inpatients	Cardiio Rhythm algorithm (supervised support vector machine)	The Cardiio Rhythm algorithm discriminated AF from sinus rhythm with 95% sensitivity, 96% specificity, PPV 92%, and NPV 97%
Attia et al[12]	Predicting dofetilide plasma concentration	Serial ECGs from 42 healthy subjects receiving either dofetilide or placebo, with training on 30 subjects and testing on 12 subjects	Supervised deep learning (CNN)	Deep learning output correlated with dofetilide concentration ($r = 0.85$) better than QTc ($r = 0.64$)

Attia et al[13]	Estimating age and sex from ECG	Trained on ECGs from 499,727 patients, and tested on ECGs from 275,056 patients	Supervised deep learning (CNN)	Accurate sex classification (AUC = 0.97) and age estimation (R-squared = 0.7, average error 6.9 years)
Ko et al[14]	Detect hypertrophic cardiomyopathy (HCM) on ECG	Trained on ECGs from 2,448 HCM cases and 51,153 controls, and tested on ECGs from 612 HCM cases and 12,788 controls.	Supervised deep learning (CNN)	Predicted HCM with an AUC of 0.96
Sengupta et al[15]	Diagnosing abnormal myocardial relaxation from time-frequency analysis of surface ECG	Continuous wavelet transform time-frequency energies of ECGs from 188 patients with corresponding tissue Doppler echocardiography	Supervised random forest cross-validation	Prediction of abnormal myocardial relaxation on tissue Doppler imaging with an AUC of 0.91
Howard et al[16]	Identification of cardiac rhythm device manufacturer and model on radiograph	Trained on 1,451 radiographs and tested on 225 radiographs	Supervised deep learning (CNN)	99.6% accuracy in identifying device manufacturer and 96.4% accuracy in identifying device model, superior to identification by cardiologists (median accuracy 72%)
Perez et al[17]	Prediction of cardiovascular mortality using discrete ECG features	Trained on 132 discrete ECG features and four demographic characteristics from 9,122 patients and assessed on 2,189 patients who underwent exercise treadmill	Supervised artificial neural network	Among patients who were classified as intermediate risk by Duke Treadmill Scoring, the third tertile of the neural network score demonstrated an adjusted Cox hazard ratio of 5.4 compared to the

		testing		first tertile
Perez et al[18]	Smartwatch identification of atrial fibrillation	PPG pulse sensor data from Apple watch were evaluated on 419,297 participants, and compared to ECG patch recordings on 450 patients	Apple irregular rhythm detection algorithm	Among participants who received notification of an irregular pulse, 34% had atrial fibrillation on subsequent ECG patch readings and 84% of notifications were concordant with atrial fibrillation
Guo et al[19]	Smart device identification of atrial fibrillation	PPG pulse sensor data from Huawei wristbands and wristwatches were evaluated on 187,912 individuals, with clinical evaluation in 262 individuals	Huawei irregular pulse detection algorithm	227 individuals (87%) were confirmed as having AF, with the positive predictive value of PPG signals being 92%.
Tison et al[20]	Automated ECG segmentation with subsequent application toward creating patient ECG profiles to detect a variety of diseases	For ECG segmentation, 170 ECGs were used for training and 36186 ECGs were used for testing. 725-component ECG profiles built from the segmented ECGs were used to develop models for disease detection	Supervised deep learning for ECG segmentation (CNN), and supervised gradient boosted machine for disease detection	Automated ECG measurements agreed with clinical measurements, and model performance for disease detection demonstrated an AUC of 0.94 for pulmonary arterial hypertension, 0.91 for hypertrophic cardiomyopathy, 0.86 for cardiac amyloid, and 0.77 for mitral valve prolapse
Raghunath et al[21]	Prediction of 1-year mortality from 12-lead ECG waveforms	1,169,662 12-lead resting ECGs obtained from 253,397 patients were used for training, and a separate	Supervised deep learning (CNN)	The model predicted 1-year mortality with very good performance (AUC 0.88), even among ECGs interpreted as normal by

		set of 168,914 patients was used for testing		physicians (AUC 0.85)
Predicting response to therapy				
Kalscheur et al[22]	Predicting CRT outcomes	Trained using clinical variables from 481 CRT-P patients and tested on 595 CRT-D patients from the COMPANION trial	Supervised random forest	Predicted death or heart failure hospitalization within 12 months with an AUC of 0.74. Top and bottom quartiles had an 8-fold difference in all-cause mortality
Feeny et al[23]	Predicting CRT outcomes	Trained using clinical variables from 470 CRT patients, tested on 455 CRT patients	Supervised naïve Bayes	Predicted echocardiographic CRT response better than current guidelines (AUC: 0.70 vs. 0.65) and had greater discrimination of long-term survival (c-index: 0.61 vs. 0.56)
Hu et al[24]	Identifying patients with reduced CRT benefit (<0% improvement in left ventricular ejection fraction or death by 18 months)	Trained on 790 CRT patients using clinical variables and two-word sequences extracted from clinical notes via natural language processing, and tested on 200 CRT patients	Supervised gradient boosting machine	Predicted reduced CRT benefit with an AUC of 0.75, and identified 26% of patients with reduced benefit at a PPV of 0.79 and accuracy of 0.65

Tokodi et al[25]	Predicting 1-, 2-, 3-, 4-, and 5-year mortality after CRT	Trained on 1510 CRT patients using 33 clinical variables and tested on an independent cohort of 158 patients	Supervised random forest	Predicted 1-, 2-, 3-, 4-, and 5- year mortality with an AUC of 0.77, 0.79, 0.78, and 0.80, respectively, with predictions superior to other pre-existing clinical risk scores
Novel characterization of disease				
Cikes et al[26]	Heart failure phenogroups in CRT	Echocardiographic volume and deformation traces and clinical variables from 1106 patients from the MADIT-CRT trial	Unsupervised multi-kernel dimensionality reduction and k-means clustering	Four phenogroups were identified with significantly different clinical and echocardiographic characteristics. Two phenogroups had substantially better treatment effect from CRT-D (reduced all-cause death or heart failure event).
Inohara et al[27]	Atrial fibrillation clinical phenotypes	Clinical variables of 9749 patients with AF in the ORBIT-AF registry	Unsupervised hierarchical agglomerative clustering	Four clinical phenotype clusters were identified (low comorbidity, behavioral comorbidity, device implantation, and atherosclerotic comorbidity) with distinct associations with clinical outcomes
Zahid et al[28]	Locating re-entrant drivers in atrial fibrillation from spatial patterns of fibrosis	Simulations of programmed electrical stimulation using 20 patient-derived 3D atrial models from MRI	Supervised support vector machine	Machine learning of MRI maps of fibrosis density and entropy classified re-entrant driver regions with an AUC of 0.91

McGillivray et al[29]	Locating re-entrant drivers in atrial fibrillation from simulations	Electrogram simulations by models of atrial myocardium structure and electro-physiological action of fibrosis	Supervised random forest	Located 95% of drivers in tissues containing a single driver, and 95% (93%) for the first (second) driver in tissues containing two drivers of AF
Varela et al[30]	3D characterization of left atrial geometry to predict post-ablation AF recurrence	3D statistical shape models of the left atrium on MRI of 144 AF patients	Supervised linear discriminant analysis	Vertical asymmetry metric in combination with left atrial sphericity predicted post-ablation recurrence at 12 months with an AUC of 0.71
Bieging et al[31]	3D characterization of left atrial geometry to predict post-ablation AF recurrence	Particle-based shape models of the left atrium on MRI of 254 AF patients	Supervised LASSO Cox regression	Addition of shape features to a Cox regression model including clinical parameters and left atrial fibrosis increased the model's concordance statistic from 0.68 to 0.72 ($p < 0.05$)
Lyon et al[32]	Identification of distinct ECG phenotypes in hypertrophic cardiomyopathy	Mathematical models of waveform morphology on high-fidelity 12-lead Holter ECGs from 85 hypertrophic cardiomyopathy patients and 38 healthy volunteers	Multi-cluster feature selection followed by Laplacian eigenmaps dimensionality reduction followed by a density-based clustering algorithm (unsupervised)	Based on QRS and T wave morphology, four ECG phenotypes were identified. Group 1A, which had primary T wave inversion, had increased hypertrophic cardiomyopathy risk scores and a predominance of coexisting septal and apical hypertrophy.

Okada et al[33]	Using fibrosis patterns to assess risk of ventricular arrhythmia in ischemic cardiomyopathy	Gadolinium-enhanced MRIs of 122 ischemic cardiomyopathy patients were used to train a model to predict arrhythmia using a spatial complexity profile of scar, and evaluated over repeated runs of cross-validation	Supervised support vector machine	Ventricular arrhythmia was classified with 81% overall accuracy and correctly classified 86% of those without ventricular arrhythmia. Overall negative predictive value was 91%.
Han et al[34]	Characterizing AF burden signatures to predict near-term stroke	30 days of cardiac implantable electronic device remote monitoring data in 3114 nonstroke controls and 71 stroke cases	Supervised machine learning (CNN, random forest, L1 regularized logistic regression)	Combining CHA2DS2-VASc with random forest and convolutional neural network yielded a validation AUC of 0.696 and test AUC of 0.634, while CHA2DS2-VASc alone had an AUC of 0.5 or less in both data sets.

References

1. Li Q, Rajagopalan C, Clifford GD. Ventricular fibrillation and tachycardia classification using a machine learning approach. *IEEE Trans Biomed Eng.* 2014; **61,** 1607–1613.
2. Acharya UR, Oh SL, Hagiwara Y, Tan JH, Adam M, Gertych A, Tan RS. A deep convolutional neural network model to classify heartbeats. *Comput Biol Med.* 2017; **89,** 389–396.
3. Teijeiro T, García CA, Castro D, Félix P. Arrhythmia Classification from the Abductive Interpretation of Short Single-Lead ECG Records. *arXiv:1711.03892 [cs]* 2017; doi:10.22489/CinC.2017.166-054
4. Hannun AY, Rajpurkar P, Haghpanahi M, Tison GH, Bourn C, Turakhia MP, Ng AY. Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. *Nat Med.* 2019; **25,** 65–69.
5. Attia ZI, Kapa S, Lopez-Jimenez F, McKie PM, Ladewig DJ, Satam G, Pellikka PA, Enriquez-Sarano M, Noseworthy PA, Munger TM, et al. Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram. *Nat Med.* 2019; **25,** 70–74.
6. Galloway CD, Valys AV, Shreibati JB, Treiman DL, Petterson FL, Gundotra VP, Albert DE, Attia ZI, Carter RE, Asirvatham SJ, et al. Development and Validation of a Deep-Learning Model to Screen for Hyperkalemia From the Electrocardiogram. *JAMA Cardiol.* 2019; **4,** 428–436.
7. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ, Carter RE, Yao X, Rabinstein AA, Erickson BJ, 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.

8. Tison GH, Sanchez JM, Ballinger B, Singh A, Olgin JE, Pletcher MJ, Vittinghoff E, Lee ES, Fan SM, Gladstone RA, et al. Passive Detection of Atrial Fibrillation Using a Commercially Available Smartwatch. *JAMA Cardiol.* 2018; **3,** 409–416.
9. Wasserlauf J, You C, Patel R, Valys A, Albert D, Passman R. Smartwatch Performance for the Detection and Quantification of Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2019; **12,** e006834
10. Bumgarner JM, Lambert CT, Hussein AA, Cantillon DJ, Baranowski B, Wolski K, Lindsay BD, Wazni OM & Tarakji KG. Smartwatch Algorithm for Automated Detection of Atrial Fibrillation. *J. Am. Coll. Cardiol.* 2018; **71,** 2381–2388
11. Yan BP, Lai WHS, Chan CKY, Chan SCH, Chan LH, Lam KM, Lau HW, Ng CM, Tai LY, Yip KW, et al. Contact-Free Screening of Atrial Fibrillation by a Smartphone Using Facial Pulsatile Photoplethysmographic Signals. *J Am Heart Assoc.* 2018; **7,** e008585.
12. Attia ZI, Sugrue A, Asirvatham SJ, Ackerman MJ, Kapa S, Friedman PA, Noseworthy PA. Noninvasive assessment of dofetilide plasma concentration using a deep learning (neural network) analysis of the surface electrocardiogram: A proof of concept study. *PLoS One.* 2018; **13.**
13. Attia ZI, Friedman PA, Noseworthy PA, Lopez-Jimenez F, Ladewig DJ, Satam G, Pellikka PA, Munger TM, Asirvatham SJ, Scott CG, et al. Age and Sex Estimation Using Artificial Intelligence From Standard 12-Lead ECGs. *Circ Arrhythm Electrophysiol.* 2019; **12,** e007284.
14. Ko WY, Siontis KC, Attia ZI, Carter RE, Kapa S, Ommen SR, Demuth SJ, Ackerman MJ, Gersh BJ, Arruda-Olson AM, et al. Detection of Hypertrophic Cardiomyopathy Using a Convolutional Neural Network-Enabled Electrocardiogram. *J Am Coll Cardiol.* 2020; **75,** 722–733.
15. Sengupta PP, Kulkarni H, Narula J. Prediction of Abnormal Myocardial Relaxation From Signal Processed Surface ECG. *J Am Coll Cardiol.* 2018; **71,** 1650–1660.

16. Howard JP, Fisher L, Shun-Shin MJ, Keene D, Arnold AD, Ahmad Y, Cook CM, Moon JC, Manisty CH, Whinnett ZI, et al. Cardiac Rhythm Device Identification Using Neural Networks. *JACC Clin Electrophysiol.* 2019; **5,** 576–586.
17. Perez MV, Dewey FE, Tan SY, Myers J, Froelicher VF. Added Value of a Resting ECG Neural Network That Predicts Cardiovascular Mortality. *Annals Noninvasive Electrocardiol.* 2009; **14,** 26–34.
18. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane A, Cheung L, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *New Engl J Med.* 2019; **381,** 1909–1917.
19. Guo Y, Wang H, Zhang H, Liu T, Liang Z, Xia Y, Yan L, Xing Y, Shi H, Li S, et al. Mobile Photoplethysmographic Technology to Detect Atrial Fibrillation. *J Am Coll Cardiol.* 2019; **74,** 2365–2375.
20. Tison GH, Zhang J, Delling FN, Deo RC. Automated and Interpretable Patient ECG Profiles for Disease Detection, Tracking, and Discovery. *Circ Cardiovascular Quality and Outcomes.* 2019; **12,** e005289
21. Raghunath S, Ulloa Cerna AE, Jing L, vanMaanen DP, Stough J, Hartzel DN, Leader JB, Kirchner HL, Stumpe MC, Hafez A, et al. Prediction of mortality from 12-lead electrocardiogram voltage data using a deep neural network. *Nat Med.* 2020; doi:10.1038/s41591-020-0870-z.
22. Kalscheur MM, Kipp RT, Tattersall MC, Mei C, Buhr KA, DeMets DL, Field ME, Eckhardt LL, Page CD. Machine Learning Algorithm Predicts Cardiac Resynchronization Therapy Outcomes: Lessons From the COMPANION Trial. *Circ Arrhythm Electrophysiol.* 2018; **11,** e005499.
23. Feeny AK, Rickard J, Patel D, Toro S, Trulock KM, Park CJ, LaBarbera MA, Varma N, Niebauer MJ, Sinha S, et al. Machine Learning Prediction of Response to Cardiac Resynchronization Therapy. *Circ Arrhythm Electrophysiol.* 2019; **12,** e007316.

24. Hu S-Y, Santus E, Forsyth AW, Malhotra D, Haimson J, Chatterjee NA, Kramer DB, Barzilay R, Tulsky JA, Lindvall C. Can machine learning improve patient selection for cardiac resynchronization therapy? *PLOS ONE.* 2019; **14,** e0222397.
25. Tokodi M, Schwertner WR, Kovács A, Tősér Z, Staub L, Sárkány A, Lakatos BK, Behon A, Boros AM, Perge P, et al. Machine learning-based mortality prediction of patients undergoing cardiac resynchronization therapy: the SEMMELWEIS-CRT score. *Eur Heart J.* 2020; doi:10.1093/eurheartj/ehz902.
26. Cikes M, Sanchez-Martinez S, Claggett B, Duchateau N, Piella G, Butakoff C, Pouleur AC, Knappe D, Biering-Sørensen T, Kutyifa V, et al. Machine learning-based phenogrouping in heart failure to identify responders to cardiac resynchronization therapy. *Eur J Heart Fail.* 2019; **21,** 74–85.
27. Inohara T, Shrader P, Pieper K, Blanco RG, Thomas L, Singer DE, Freeman JV, Allen LA, Fonarow GC, Gersh B, et al. Association of of Atrial Fibrillation Clinical Phenotypes With Treatment Patterns and Outcomes: A Multicenter Registry Study. *JAMA Cardiol.* 2018; **3,** 54–63.
28. Zahid S, Cochet H, Boyle PM, Schwarz EL, Whyte KN, Vigmond EJ, Dubois R, Hocini M, Haïssaguerre M, Jaïs P, Trayanova NA. Patient-derived models link re-entrant driver localization in atrial fibrillation to fibrosis spatial pattern. *Cardiovasc Res.* 2016; **110,** 443–454.
29. McGillivray MF, Cheng W, Peters NS, Christensen K. Machine learning methods for locating re-entrant drivers from electrograms in a model of atrial fibrillation. *R Soc Open Sci* 2018; **5,** 172434.
30. Varela M, Bisbal F, Zacur E, Berruezo A, Aslanidi OV, Mont L, Lamata P. Novel Computational Analysis of Left Atrial Anatomy Improves Prediction of Atrial Fibrillation Recurrence after Ablation. *Front Physiol.* 2017; **8.**

31. Bieging ET, Morris A, Wilson BD, McGann CJ, Marrouche NF, Cates J. Left atrial shape predicts recurrence after atrial fibrillation catheter ablation. *J Cardiovasc Electrophysiol.* 2018; **29,** 966–972.
32. Lyon A, Ariga R, Mincholé A, Mahmod M, Ormondroyd E, Laguna P, de Freitas N, Neubauer S, Watkins H, Rodriguez B. Distinct ECG Phenotypes Identified in Hypertrophic Cardiomyopathy Using Machine Learning Associate With Arrhythmic Risk Markers. *Front Physiol.* 2018; **9.**
33. Okada DR, Miller J, Chrispin J, Prakosa A, Trayanova NA, Jones S, Maggioni M, Wu KC. Substrate Spatial Complexity Analysis for the Prediction of Ventricular Arrhythmias in Patients With Ischemic Cardiomyopathy. *Circ Arrhythm Electrophysiol.* 2020; **13,** e007975.
34. Han L, Askari M, Altman RB, Schmitt SK, Fan J, Bentley JP, Narayan SM, Turakhia MP. Atrial Fibrillation Burden Signature and Near-Term Prediction of Stroke. *Circ Cardiovasc Quality and Outcomes.* 2019; **12,** e005595.