

Artificial Intelligence Electrocardiogram
Enabled Mobile Device in Screening Families for
Dilated Cardiomyopathy (The AI-SCREENDCM
Decentralized Clinical Trial Pilot Study)

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CLINICAL RESEARCH PROTOCOL

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Abbreviations

AI	Artificial Intelligence
AE	Adverse Event
MP	Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRC	Clinical Research Coordinator
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
MOP	Manual of Procedures
PI	Principal Investigator
SAP	Statistical Analysis Plan
DSMC	Data Safety Monitoring Committee
SoA	Schedule of Activities
SOP	Standard Operating Procedure
LG Health	Lancaster General Health
LGH	Lancaster General Hospital
FDR	First-degree Relative(s)
DCM	Dilated Cardiomyopathy
ECG	Electrocardiogram
TTE	Transthoracic echocardiogram
LVEF	Left Ventricular Ejection Fraction
MC	Mayo Clinic

1 STUDY SUMMARY

1.1 Synopsis

Title:	Artificial Intelligence Electrocardiogram Enabled Mobile Device in Screening Families for Dilated Cardiomyopathy (The AI-SCREENDCM Decentralized Pilot Study)
Short Title:	AI-SCREENDCM Decentralized Clinical Trial - Pilot Study
Study Hypothesis:	Artificial Intelligence – Electrocardiogram (AI-ECG) test will increase cardiac screening by Transthoracic Echocardiogram (TTE) for first degree relatives (FDR) of patients with dilated cardiomyopathy (DCM). FDR will be contacted and offered testing with an AI-ECG enabled mobile device in addition to the current standard of care (SOC) recommendation to undergo a screening TTE.
Objectives:	The main objective is to assess the feasibility and impact of screening FDR of DCM probands using a mobile ECG with the ability to transmit the ECG for cloud-based AI analysis to detect reduced left ventricular ejection fraction (LVEF). This protocol will examine the impact of incorporating the screening AI enhanced ECG into SOC recommendations (screening TTE).
Primary Endpoint:	This study's primary endpoint is to assess the feasibility of performing AI-ECG test and the subsequent uptake of cardiac screening by TTE in FDRs of DCM patients.
Secondary Endpoint:	To detect $LVEF \leq 45\%$ by AI-ECG among FDR of DCM probands.
Exploratory Endpoints:	1. Identify barriers to adoption of AI technology, variables that contribute to the reluctance to participate, and logistical barriers to research utilizing “decline to participate” surveys. 2. To detect $LVEF \leq 45\%$ by TTE among FDR of DCM probands. 3. To assess the concordance of 6L Kardia AI ECG with 12L AI ECG to detect reduced LVEF in DCM probands
Study Population:	Mayo Clinic Group 1: 50 individuals (probands), age ≥ 18 with a diagnosis of DCM Group 2: FDR of consented proband, age ≥ 18 , who were not previously instructed to be screened, were not screened for DCM, and were not previously diagnosed with reduced LVEF Penn Medicine Research Institute at Lancaster General Hospital (LGH) Group 1: 50 individuals (probands), age ≥ 18 with a diagnosis of DCM

	Group 2: FDR of consented proband, age ≥ 18, who were not previously instructed to be screened, were not screened for DCM, and were not previously diagnosed with reduced LVEF Central Pennsylvania Clinic (CPC) Group 1: 5 individuals (proband), age ≥ 18 with a diagnosis of DCM Group 2: FDR of consented proband, age ≥ 18, who were not previously instructed to be screened, were not screened for DCM, and were not previously diagnosed with reduced LVEF
Phase:	Pilot study for parameter estimation and feasibility
Description of Sites/Facilities	AI-ECG study activities will take place mainly in participants' homes, with study team coordination taking place remotely from Mayo Clinic and the Research Institute at Lancaster General Hospital respectively. Participants recruited at the Central Pennsylvania Clinic will undergo AI-ECG study activities onsite.
Description of Study Intervention:	AI-ECG will be acquired using the 6-lead AliveCor Kardia device resulting in generation of prediction probabilities for reduced LVEF. The Kardia 6-lead device is an ambulatory, wireless device that connects to a smartphone, is readily available, and easy to use. The device is an FDA approved handheld smart device that records an ECG in 30 second to 5-minute increments. The ECG signal is communicated wirelessly via Bluetooth to a mobile computing platform (MCP) which can be a smartphone or tablet. The MCP should be running the KardiaRx application (App) to enable the ECG transfer. The KardiaRx App processes the signal acquired from the Kardia device into a real-time ECG. The Kardia 6L system can record Leads I and II simultaneously and derive Leads III, and unipolar limb leads aVR, aVL, and aVF. The results of the ECG tracings recorded by the AliveCor devices will not be entered into the electronic medical record or used to guide the participant's clinical care. ECG data from the recordings identified only by the connection code will be uploaded to the encrypted AliveCor cloud. The up-loaded ECG will be analyzed by FDA approved AI software designed to detect reduced LVEF. The KardiaStation App will be used to record Kardia 6L ECG in probands seen in the out-patient clinic setting. The probands clinical 12L ECGs will be used if recorded within 30 days of their enrollment and Kardia 6L recording. The concordance of the algorithm results applied to the Kardia 6L data with the 12L FDA approved LVEF algorithm results will be assessed.

Study Duration:	Mayo Clinic enrollment, study activities and analysis will occur approximately within 6 months after IRB approval
Participant Duration:	Approximately 3 months

2 INTRODUCTION AND RATIONALE

2.1 Background

Dilated cardiomyopathy (DCM) often leads to heart failure with reduced left ventricular ejection fraction (LVEF) and is the most common indication for heart transplantation in the United States [1]. Moreover, DCM was found to be familial in at least one in five patients by screening transthoracic echocardiogram (TTE), and 75% of these did not have a family history of DCM [2]. For this protocol's purposes, it is important to note that DCM can also present with intermediate phenotypes that do not meet standard disease definition such as LV dilatation. This lack of dilation despite reduced LVEF is seen as a manifestation of some genetic DCM phenotypes [3,4]. Therefore, a new category of hypokinetic nondilated cardiomyopathy (HNDC) defined as $LVEF \leq 45\%$ without other secondary causes, such as abnormal loading conditions or coronary artery disease, has been proposed especially to facilitate family screening in this category that is usually applicable to DCM patients [5,6] and because treatment recommendations are based on the presence of reduced LVEF alone. Subsequent reference to DCM will be inclusive of patients with HNDC.

Patients with undiagnosed DCM may present with sudden death or heart failure [6]. These deaths and morbidity due to heart failure may be preventable as DCM can be treated even when asymptomatic. Current guidelines recommend first-degree relatives (FDR) of probands or patients with DCM undergo cardiac screening with ECG and TTE. The 2013 American College of Cardiology/American Heart Association (AHA) Guidelines recommend cardiac screening with TTE of all FDR of patients with a familial history of DCM in conjunction with genetic testing and counseling. For patients with idiopathic DCM and no clear family history, a TTE screening should be discussed. A 2016 American Heart Association scientific statement reiterated the need for all FDR of patients with a familial history of DCM to undergo periodic serial echocardiographic screening and considered it reasonable to conduct such screening for FDR of patients with idiopathic DCM [7]. The 2021 European Society of Cardiology guidelines recommend clinical evaluation, ECG, and echocardiography be performed in FDR of all patients with DCM [8]. These guidelines should be interpreted especially in the context of 2 recent studies that were completed after these guidelines were issued. These recent FDR cardiac screening studies have demonstrated and confirmed DCM to be familial in 22-30% of cases not by using family history but by performing TTE screening [9,10].

Study Rationale

However, widespread implementation of such cardiac screening is limited by cost, shortage of echocardiography technical expertise in the general community, and lack of motivation especially in asymptomatic family members confronting logistic issues for making arrangements to undergo cardiac screening. Screening with genetic testing, particularly in FDR has also been limited due to similar issues, in addition to privacy concerns and limited applicability of genetic testing for screening of FDR given the 10-40% yield of genetic testing in the proband [1]. Importantly even if FDR are diagnosed to be genetic carriers, they may not have medically actionable reduced LVEF. An artificial intelligence (AI)-based algorithm has been developed and validated to detect reduced LVEF including in DCM patients [11] which could be used for screening FDR of the patient or proband with DCM using a 6-lead ECG obtained with AliveCor Kardia 6-lead, a hand-held ECG device.

This protocol intends to evaluate the use of a portable ECG device recording analyzed by an AI-ECG algorithm for detection of reduced LVEF. The AI-ECG algorithm using the 12-lead has recently been accepted for medical use by the US Food and Drug Administration. The AI-ECG algorithm using the 6-lead device, used in this protocol, is now investigational. In this study the concordance of the reduced LVEF AI ECG algorithm applied to Kardia 6L ECGs with the 12L FDA approved AI ECG will be assessed.

2.2 Preliminary Data and Validation Studies

A convolutional neural network deep learning algorithm has been developed at Anumana, a partnership with Mayo Clinic and nference, to identify reduced LVEF using an ECG alone with high discrimination – area under the curve (AUC) of 0.93 (**Figure 1**). The initial model was developed and validated using a dataset of 97,829 patients (with paired ECG and echocardiograms) [16]. This algorithm has been also validated prospectively in the form of a randomized clinical trial resulting in >30% increased detection of reduced LVEF by TTE in a primary care setting [17]. Subsequently, alternative LVEF thresholds have been used and validated successfully including for DCM patients. For detection of $LVEF \leq 45\%$, the AUC in DCM patients was 0.955 with a sensitivity of 98.8% and specificity 44.8% with a high negative predictive value of almost 100% thus demonstrating that the AI-ECG could be used as a simple and cost-effective screening tool for screening FDR of DCM patients [15].

We simulated AI-ECG screening of FDR of DCM patients (**Figure 2**) using a previously published echocardiography-based FDR screening study. We demonstrate that for the 325 FDR of 59 index DCM cases, AI-ECG would have detected reduced $LVEF \leq 45\%$ in 183 FDR of which 18 with DCM would be identified by TTE. However, AI-ECG would be negative in the remainder 142 FDR who would not need TTE thus potentially resulting in significant cost savings as opposed to a strategy of performing screening TTE in all FDR. Although the algorithm was developed using 12-lead ECG data, it has been successfully used and adapted to a single lead Apple watch ECG [18] with an AUC of 0.88 to detect reduced LVEF and therefore should perform with similar, if not better, accuracy using 6-lead ECG.

Figure 1. The ROC curve of the AI-ECG algorithm in detecting reduced LVEF

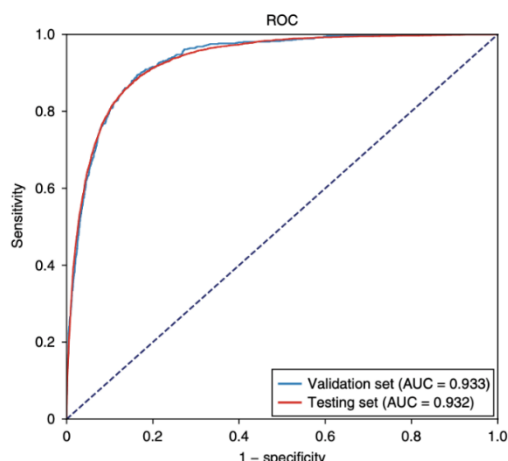
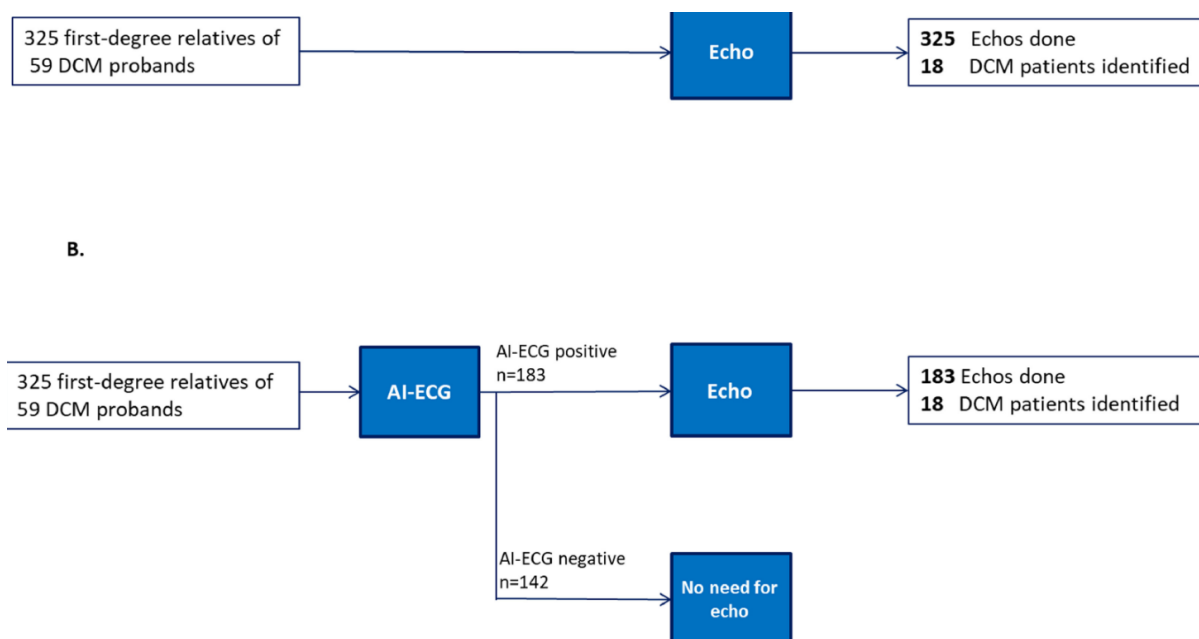


Figure 2. Simulation based on detecting DCM in FDR of probands using TTE alone and using AI-ECG directed TTE.



The Kardia 6-lead device (**Figure 3**) is an ambulatory, wireless device that connects to a smartphone, which is readily available, and easy to use. The device is an FDA-approved handheld smart device that records an ECG in 30 second to 5-minute increments. The ECG signal is communicated wirelessly via Bluetooth to a mobile computing platform (MCP), which can be a smartphone or tablet. The MCP should be running the KardiaRx application (App) to enable the ECG transfer. The KardiaRx App processes the signal acquired from the Kardia device into a real-time ECG. The Kardia 6L system can record Leads I and II simultaneously and

derive Leads III and unipolar limb leads aVR, aVL, and aVF. The mobile or web-based app can only be used after inputting a 12-character connection code that will be uniquely assigned to each study ID, hence connecting the research participant to the AI-ECG.



Figure 3. AliveCor 6L wireless ECG device with portable 6-lead ECG displayed

This study aims to prospectively demonstrate that asking probands to contact their FDR and offering AI-ECG to FDR is feasible and an effective strategy to increase the uptake of definitive diagnostic testing by TTE.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To determine the feasibility and impact of AI-ECG on the adoption of TTE recommendations for FDRs of patients with DCM	The number of consented FDR who successfully undergo AI ECG For this study, the following screening procedures will be considered a valid cardiac screening attempt: • Scheduled or Completed TTE • Scheduled or completed clinician visit for the purposes of generating a cardiac evaluation Documentation of such a scheduled or completed clinician visit and/or TTE within 1-6 months of contact of study team
Secondary	
To screen for LVEF $\leq 45\%$ by AI-ECG among FDR of DCM probands.	Positive AI-ECG screens/total population of those undergoing AI-ECG
Exploratory	
1. Identify and analyze barriers to adoption of AI technology, variables that contribute to the reluctance to participate, and logistical barriers to research 2. To detect LVEF $\leq 45\%$ by TTE among FDR of DCM probands	1. Collect “decline participation” surveys 2. Positive TTE screens/total number of FDR undergoing TTE 3. Comparison of AI ECG reduced LVEF algorithm results between 6L Kardia ECG and 12L AI ECG in DCM probands

4 MAYO CLINIC (MC) STUDY PLAN

4.1 Study Design

- Pilot study for parameter estimation and feasibility
 - Under intention to treat, the percentage of FDR engaged in cardiac screening will be calculated.
- End of Study Definition**

A participant is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Events (Section 6.3).

5 STUDY POPULATION

5.1 Inclusion Criteria

5.1.1 *Inclusion Criteria (Proband)*

- Male or female age ≥ 18 years
- Confirmed diagnosis of DCM determined at the discretion of the treating physician and defined as LVEF $\leq 45\%$ at any time during the clinical course of the patient
- Must have at least one living ≥ 18 years FDR
- Able to provide informed consent

5.1.2 *Inclusion Criteria (FDR)*

- Male or female age ≥ 18 years who are first-degree relatives of patients with DCM
- Proband has provided informed consent
- FDR able to provide informed consent
- Access to a smartphone or digital tablet with cellular data or Wi-Fi access

5.2 Exclusion Criteria

5.2.1 *Exclusion Criteria (Proband)*

- DCM attributed to any other secondary form of cardiomyopathy per the investigator's determination
 - Proband has previously informed FDR to undergo cardiac screening
 - Ischemic cause of reduced LVEF
 - evidence of myocardial infarction, inducible ischemia or chest pain on stress testing in absence of coronary angiogram to rule out ischemic disease
 - history of acute coronary syndromes (STEMI, NSTEMI or unstable angina) revascularization or $\geq 75\%$ stenosis of either left main or LAD or $\geq 75\%$ stenosis of 2 major epicardial vessels on angiogram
 - Moderate or greater primary valvular abnormality not due to underlying cardiomyopathy
 - Congenital structural heart disease
 - Severe and untreated or untreatable hypertension
 - Cardiomyopathy due to acute or reversible conditions; examples include tachyarrhythmias, thyroid disorders, iron overload
 - Any secondary cause of reduced LVEF such as peripartum cardiomyopathy, myocarditis, amyloidosis, sarcoidosis, exposure to toxins including alcohol, substance abuse or chemotherapeutic drug
 - (CPC Participants only) Home address outside of traveling range
-

5.2.2 Exclusion Criteria (FDR)

- Previously informed about cardiac screening or has completed cardiac screening by TTE
- Previously diagnosed with reduced LVEF
- (CPC Participants only) Home address outside of traveling range

5.3 Schema

On overview of participant study activities is outlined in **Figure 4** and described in detail in the proceeding sections.

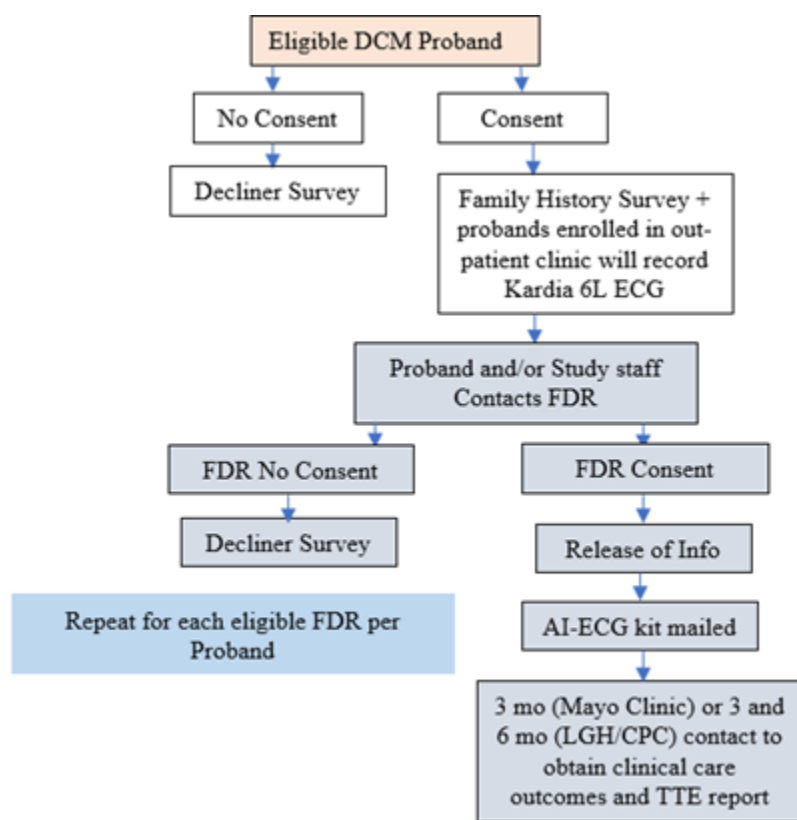


Figure 4: Participant selection and enrollment workflow overview

5.4 Recruitment, Enrollment and Consent – Probands and FDR (Mayo Clinic)

1. Patients with DCM (probands) will be identified in one of two ways: (1) retrospectively via chart review or (2) prospectively via outpatient clinic visits.
2. Probands identified retrospectively will be contacted by sending a message to their email, patient portal, and/or initial contact by phone. The message may have a link to a REDCap

survey embedded for them to indicate their interest, eligibility, and their availability for a time to discuss the consent form by phone.

3. Probands identified prospectively may either be approached during an outpatient clinic visit, by phone, and/or by email. Providers and/or clinical staff may introduce the study to patients to gauge initial interest.

- These methods may be used to initiate the recruitment process 1) in outpatient clinic 2) phone call to introduce the study, or 3) emailing the contact form to be completed with best time for study staff to contact the proband to review screening criteria, provide additional information regarding the study and enrollment. Study staff may then proceed with consent and CRF data collection by phone if the proband is interested. Proband will be asked to either contact their FDR to ask if they would like to participate and then send study staff FDR information or directly provide their FDR contact information for study staff to contact. Name, address and other pertinent information may be collected from the FDR so the kit containing the AliveCor Kardia 6L device may be sent to the consented and enrolled FDR. If FDRs decline participation their contact information provided by the proband will be destroyed and they will be asked to complete a decliner survey either by phone or by email, depending on their preference. Probands consented in the out-patient setting will be asked to record a 30-second hand-held Kardia 6L ECG.

4. Consent documents will be Institutional Review Board (IRB)-approved and the participant will be asked to review the consent document. The study team will explain the information in the consent form and answer any questions. An electronic copy of the informed consent document will be provided to the participants for their records.

5. After the proband consents to participate, they may send a REDCap link to their FDR which includes study details for them to indicate interest, eligibility, and their availability for a phone call to discuss additional information about the study and enrollment. Or the proband may share their FDR contact information and the study team may call and/or send the FDR contact form through REDCap.

6. For probands that indicate in the contact form that they are not interested in participating, they will be presented with the option to complete a decliner survey asking them to share why they are unwilling to participate or if on a call with proband when they decline, ask if they would fill out the REDCap decliner survey on the phone, by email or not at all.

7. After identifying whether the FDR is interested, the study team will utilize a different IRB approved consent form to review and provide study direction to the FDR. The FDR will also be asked to sign a release of information (ROI), sent electronically for signing via Part 11 compliant Adobe e-signature account for all non-Mayo Clinic participants. The release will authorize study staff to access medical records from the participants' healthcare institution. The records needed include clinical care outcomes and echocardiogram results.

8. The study team will mail a Kardia device with instructions for the FDR to record and transmit the Kardia 6L ECG and the study staff will schedule a time upon its arrival to ensure the FDR is comfortable taking the ECG and ensuring a quality recording is transmitted.

9. There will be no compensation for study participation.

5.6 Recruitment, Enrollment and Consent – Probands (LGH)

1. Patients with DCM (probands) will be identified in one of two ways: (1) retrospectively via chart review or (2) prospectively via outpatient clinic visits at LG Health.
2. Probands identified retrospectively will be contacted by sending a message to their email, patient portal, and/or initial contact by phone. The message will have a link to a REDCap survey embedded for them to indicate their interest, eligibility, and their availability for a time to discuss the consent form by phone.
3. Probands identified prospectively may either be approached during an LG Health clinic visit (such as The Heart Group), by phone, and/or by email. Recruitment posters will be posted in clinical patient rooms, waiting areas and other areas at LG Health locations. Providers and/or clinical staff will introduce the clinical trial to patients to gauge initial interest. Additionally, interested patients may scan a QR code located on the recruitment poster to review study information and provide contact information if interested in being screened for participation.
4. After referral or contact form completion and screening criteria have been reviewed, a Clinical Research Coordinator (CRC) will contact the proband to provide additional information regarding the study and enrollment.
5. Consent documents will be Institutional Review Board (IRB)-approved and the patient will be asked to review the document. The study team will explain the information in the consent form and answer any questions. An electronic copy of the informed consent document will be provided to the participants for their records. The informed consent process will be conducted and documented in REDCap (including the date) before the participant undergoes any study-specific activities.
6. After the proband consents to participate, they will send a REDCap link to their FDR which includes study details for them to indicate interest, eligibility, and their availability for a phone call to discuss additional information about the study and enrollment.
7. For probands that indicate in the contact form that they are not interested in participating, they will be presented with the option to complete a decliner survey asking them to share why they are unwilling to participate.
8. There will be no compensation for study participation.

5.7 Recruitment, Enrollment and Consent – Probands (Central PA Clinic)

1. Patients with DCM (probands) will be identified in one of two ways: (1) retrospectively via chart review or (2) prospectively via outpatient clinic visits at CPC.
2. Probands identified retrospectively will be contacted by sending a message to their home address, email, patient portal, and/or initial contact by phone. The message will have a link to a REDCap survey embedded for them to complete electronically. The proband can also

contact CPC and complete the survey over the phone or in person with study staff. The survey will indicate their interest, eligibility, and their availability for a time to discuss the consent form by phone or in person.

3. Probands identified prospectively may be approached during a CPC clinic visit, by phone, by email, and/or by mail. Recruitment posters will be posted in clinical patient rooms, waiting areas, and other areas at CPC. Providers and/or clinical staff will introduce the clinical trial to patients to gauge initial interest. Study information may also be sent home with the patient for later review. Additionally, interested patients may scan a QR code located on the recruitment poster to review study information and provide contact information if interested in being screened for participation.
4. After referral or contact form completion and screening criteria have been reviewed, a study team member will contact the proband to provide additional information regarding the study and enrollment.
5. Consent documents will IRB-approved and the patient will be asked to review the document. The study team will explain the information in the consent form and answer any questions. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date) before the participant undergoes any study-specific activities.
6. After the proband consents to participate, the study team will provide probands with details on how their FDR can contact the study team for potential enrollment.
7. For probands that indicate in the contact form or to study staff that they are not interested in participating, they will be presented with the option to complete a decliner survey. The decliner survey will ask them to anonymously share why they are unwilling to participate.
8. There will be no compensation for study participation.

5.8 Recruitment, Enrollment and Consent – FDR (LGH)

1. Consent documents will be Institutional Review Board (IRB)-approved and the participant will be asked to review the document. The study team will explain the information in the consent form and answer any questions. An electronic copy of the informed consent document will be provided to the participants. The informed consent process will be conducted and documented in the source document (including the date) before the participant undergoes any study-specific activities.
2. Demographic questions will be asked after consent is obtained.
3. A release of information (ROI) will also be sent electronically for signing via Part 11 compliant Adobe e-signature account for all non-LG Health participants. The release will authorize study staff to access medical records from the participants' healthcare institution. The records needed include clinical care outcomes and echocardiogram results.

4. The study team will contact the probands to request that they contact their FDR to encourage them to obtain cardiac screening by TTE.
5. The FDR will have the option to obtain a 12-Lead ECG which will be acquired at an LGH outpatient location.
6. The study team will contact the FDR and mail a Kardia device with instructions to record and transmit the mobile ECG to the study staff.

5.9 Recruitment, Enrollment and Consent – FDR (Central PA Clinic)

1. Consent documents will be IRB-approved, and the participant will be asked to review the document. The study team will explain the information in the consent form and answer any questions. A copy of the informed consent document will be provided to the participants. The informed consent process will be conducted and documented in the source document (including the date) before the participant undergoes any study-specific activities.
2. Demographic questions will be asked after consent is obtained.
3. FDRs will complete a 12-Lead ECG, if obtainable, at the Central PA Clinic.
4. Study team will provide a Kardia device and instructions on use to FDRs.
5. FDRs will complete the Kardia mobile ECG transmission with assistance of a study team member.
6. Study team will ask the FDR if they would like a limited TTE performed, which will be coordinated at the patient's request.

6 STUDY INTERVENTION ADMINISTRATION

6.1 Study Intervention Description – Proband Family History Survey

Upon participant consent, the study team will ask proband participants to either complete the survey together over the phone or if they prefer to have the survey sent. Each proband participant will receive a demographics survey and family history survey via REDCap. The family history survey includes a series of questions to gather information on their family's heart health history. The survey will ask questions regarding their first-degree relative's vital status, known diagnosis of heart disease, and whether cardiac screening was previously performed. The study team may follow-up with participants via phone or electronic messaging to remind them to complete the surveys and discuss any responses that need further completion. The KardiaStation App will be used to record Kardia 6L ECG in probands seen in the out-patient clinic setting. The probands clinical 12L ECGs will be used if recorded within 30 days of their enrollment and Kardia 6L recording. The quality of the algorithm results applied to the Kardia 6L data will be assessed and compared to the 12L FDA approved LVEF algorithm results. Medical information in the probands medical record may also be used for information pertinent to the study. If the proband declines participation, study staff will request the proband to fill out a decliner survey either by

phone during initial assessment of interest or by email depending on how the participant responds to the invitation to participate.

6.2 Study Intervention Description – FDR or Proband 12-Lead ECG

Upon participant consent, only those probands or FDR having a 12-Lead ECG as part of their routine clinical care at LGH or Central PA may have their ECG sent to Mayo Clinic for LVEF analysis. If a 12-Lead ECG is acquired at LGH or Central PA study teams will share the deidentified data (with subject study ID) with Mayo Clinic via secure file-sharing practices.

6.3 Study Intervention Description – FDR KardiaRx ECG Screening (MC and LGH)

1. (MC & LGH Participants Only) The study team will mail all FDR participants a kit which will include the mobile device and relevant instructions such as: how to download the app, complete the ECG reading, and mail back the device.
2. (MC & LGH Participants Only) Participants will download the KardiaRx research app on a smart phone or tablet and input their unique connection code provided to MC and LGH by AliveCor. The study staff may call participants to review the Kardia 6L ECG recording instructions and verify the recording was acquired and the signal to noise quality was sufficient. If needed, multiple transmissions may be requested to ensure quality transmission based on study staff discretion.
3. (CPC Participants Only) The study team will download the KardiaStation research app on a smart phone or tablet and input the participant's study id assigned by the study team to correlate back to the patient enrolled. The study staff will help the participants complete the Kardia 6L ECG recording and verify that the recording was acquired and the signal to noise quality was sufficient. If needed, multiple transmissions may be requested to ensure quality transmission based on study staff discretion.
4. The AliveCor Kardia 6L ECG recordings recorded by Mayo Clinic FDR will be identifiable only by Mayo Clinic study staff using the 12-digit connection code, study ID and date of transmission. AliveCor Kardia 6L ECG recordings taken by LG study staff will be identifiable to LG Health study staff only using the participant assigned connection code, study ID, and the date of transmission. All sites ECG data will be accessible from the AliveCor cloud for subsequent download to the Mayo Clinic secured server for LVEF analysis. The MC and LG Health study staff will then be able to match the connection code to the study ID of the participant.
5. 6L ECG data may be downloaded from the AliveCor cloud to be reviewed and interpreted by study staff (MC and LGH Staff).
6. The transmitted ECG will be interpreted by the LVEF AI-ECG algorithm after being downloaded to the secure Mayo Clinic server. After AI-ECG analysis is completed, results will be shared to Mayo Clinic participants. Mayo Clinic will send a weekly report electronically to LGH and CPC and results will be shared electronically or verbally to the participant. ECGs will not be interpreted in real time. Participants will be notified that the purpose of the ECG transmission is for research only and will not be used for clinical

care. If the participant has questions, they may contact the study staff who will only be able to reiterate the information previously shared and also recommend that they reach out to their healthcare provider with questions.

7. The results of the ECG tracings recorded by the AliveCor devices will not be entered into the electronic medical record or used to guide the participants' clinical care.
8. Upon completion of transmission, participants will be instructed to return the device to the study staff.
9. Approximately at 30 to 60 days at MC and 3 and 6 months at LGH after the enrollment date, the study staff will contact the study participants to assess the following:
 - a. Whether a TTE was requested or obtained. If obtained, results will be documented by acquiring information from the TTE report. A release of information will be obtained from the FDR in order to contact the institution where they were seen for medical care or TTE was performed.
 - b. Results of the TTE will be documented in REDCap.
10. The study coordinators will request specific results documentation from the participants or the medical institution at which the TTE was performed via HIPAA compliant email (TTE report) or secure fax. Upon documentation of results by study staff in REDCap, the source email/echocardiogram data will be saved electronically in the secure research server for source documentation.

6.4 Study Intervention Description – FDR KardiaStation ECG Screening (Central PA Clinic)

1. The study team will download the KardiaStation research app on a smart phone or tablet and input the participant's unique study id. The study staff will help the participants complete the Kardia 6L ECG recording and verify that the recording was acquired and the signal to noise quality was sufficient. If needed, multiple transmissions may be requested to ensure quality transmission based on study staff discretion.
2. The AliveCor Kardia 6L recordings will be identifiable to LG Health study staff only using the study ID, and the date of transmission. ECG data will be accessible from the AliveCor cloud for subsequent download to the Mayo Clinic secured server. The LG Health study staff will then be able to match the results to the study ID of the participant.
3. ECG data may be downloaded from the AliveCor cloud to be reviewed and interpreted by study staff (MC and LGH Staff).
4. The transmitted ECG will be interpreted by the LVEF AI-ECG algorithm and results will be shared electronically or verbally to the participant. ECGs will not be interpreted in real time. Participants will be notified that the purpose of the ECG transmission is for research only and will not be used for clinical care. If the participant has questions, they may contact the study staff who will only reiterate the information previously shared and recommend that they contact their healthcare provider with questions.
5. The results of the ECG tracings recorded by the AliveCor devices will not be entered into the electronic medical record or used to guide the participants' clinical care.

6. Upon completion of transmission, participants will be instructed to return the device to the study staff.
7. Approximately at 1 to 6 months after the enrollment date, the study staff will contact the study participants to assess the following:
 - a. Whether a TTE was requested or obtained. If obtained, results will be documented by acquiring information from the TTE report.
 - b. Results of the TTE will be documented in REDCap.
8. The study coordinators will request specific results documentation from the participants or the medical institution at which the TTE was performed via HIPAA compliant email (TTE report) or secure fax. Upon documentation of results by study staff in REDCap, the source email/echocardiogram data will be saved electronically in our secure research server for source documentation

6.5 Participant Withdrawal from the Study

Participants may withdraw consent or refuse intervention at any point in the study. If they withdraw participation after receiving the mailed ECG kit, they are required to send it back to the study team. If, in the opinion of the investigators, the conduct of the study is not in the best interest of the participant, the investigator may withdraw participants from the study. Refusing to participate or withdrawal from the study will not impact the participant's medical care. Withdrawal of consent will be documented as well as all data collected prior to withdrawal of consent will be submitted.

Study data collection stops upon participant withdrawal from the study. Data that has already been collected up until study withdrawal will remain part of the study database. It will be documented whether each participant completes the study.

6.6 Schedule of Events

Tests and Procedures	Proband	FDR (AI-ECG intervention)
Informed Consent	X	X
Release of Information (ROI) from those who are not MC or LGH patients for echocardiography report		X
Demographics including clinical data	X	X
Family history survey and phone call with study team	X	
12-Lead ECG ¹		X
AI-ECG transmission with study staff support (proband enrolled in out-patient clinic)	X	X
Collect transthoracic echocardiogram results		X

Contact by study staff ²		X
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1 Optional 12-Lead EKG can be completed at LGH or Central PA Clinic within 30 days +/- or on the same day as the AI-ECG.

2 For the visits as applicable, the study staff will call FDR at approximately 30 to 60 days (MC) and 3 months (LGH) to determine whether they pursued evaluation based on propensity for DCM. If FDR has not, but plans to pursue assessment, record their plans. Study staff contact again at approximately 6 months (LGH and CPC). If FDR does not plan to pursue assessment, study staff will assess if there is a known reason.

7 STATISTICAL CONSIDERATIONS

7.1 General Approach

This prospective clinical trial will involve clustered enrollment of first-degree relatives (FDR) for each enrolled index (proband) cases of DCM. The cluster size is expected to vary widely. The minimum cluster size based on the eligibility criteria is 1. Some family units may have 10 or more FDR. We expect there to be a non-negligible correlation of engagement in screening within clusters.

7.2 Primary Hypothesis

The aim of this study is to prospectively demonstrate that asking probands to contact their FDR and offering an AI-ECG strategy to FDR is an effective method to increase the uptake of cardiac screening to detect DCM. The primary objective is defined around the concept of feasibility. This includes measuring the engagement rate into the screening program in order to design a comparative and confirmatory RCT that compares the AI-enhanced screening to standard of care (future study).

7.3 Primary Endpoints

ENDPOINTS
Primary
To determine the feasibility and impact of AI-ECG on the adoption of TTE recommendations for FDRs of patients with DCM
Secondary
To screen for LVEF $\leq 45\%$ by AI-ECG among FDR of DCM probands.
Exploratory
1. Identify and analyze barriers to adoption of AI technology, variables that contribute to the reluctance to participate, and logistical barriers to research 2. To detect LVEF $\leq 45\%$ by TTE among FDR of DCM probands 3. To assess the concordance of 6L Kardia AI ECG with 12L AI ECG to detect reduced LVEF in DCM probands

7.4 Analysis Sets and Endpoint Operationalization

The analysis will be largely focused on descriptive analysis since the study is uncontrolled. These descriptive analyses will largely serve to inform the design of the subsequently planned randomized comparative study.

The numerator for the primary endpoint is the number of FDRs that engage in the screening as described above. The denominator for the primary endpoint will be the enumeration of all FDRs supplied by the probands. Confirmation of engagement in DCM screening (the “numerator”) is expected to be obtained only from consented participants. Declination to provide informed consent will be considered failure to screen for the primary analysis.

7.5 Primary Endpoint Analysis

For the primary analysis, the list of FDR supplied by the index DCM case will be coded for the primary outcome as either a 1 or 0. A 1 will indicate successful engagement in a recognized screening modality; 0 will be for refusal to participate or no documented engagement in screen as specified above. Note, the results of any DCM screening tests are not considered in the primary analysis – it is simply engagement or not. Proportions along with a 95%CI will be calculated. The 95%CI will be calculated unadjusted with a normal approximation and adjusted using generalized estimating equations methods to account for the clustering within families as anchored by the proband.

7.6 Sample Size Estimation

The sample size of Probands and FDRs for the recruitment at each site is based on targeting a set of probands with enrolled ≥ 1 FDR to provide a $\pm 15\%$ margin of error for the estimation of the primary endpoint. Assuming a normal approximation to the binomial along with a conservative estimate that the engagement is 50% (i.e., region of maximal binomial error), a sample size of 50 FDRs is required. Using data provided by the Huggins, et. al. (JAMA. 2022;327(5):454-463) trial, they enrolled 3-4 FDR on average per proband with a range of 80% to 57% of probands with ≥ 1 enrolled FDR across the 4 subgroups. Thus, we are expecting between 150 and 200 FDR to be enrolled probands which provides an unadjusted margin of error of approximately $\pm 10\%$ for the primary outcome of screen rate, allowing for some loss of precision due to the clustering per site. The overall sample size is expected to be 105 probands and approximately 400 FDRs for a total sample size of human participants of approximately 505. Mayo Clinic will accrue upto 50 probands and 200 FDRs, rest of the accrual will occur at LGH and CPC.

7.7 Risk/Benefit Assessment

7.7.1 Known Potential Risks

The risks of this research study are expected to be minimal and represent the general risks associated with wellness screening and routine medical care. However, there are some risks that are associated with transmitting data and communication of the results.

Holding the AliveCor device to record electrocardiographic tracings will not cause discomfort or inconvenience. The AliveCor Kardia 6L is a 510(k) cleared device. There may be distress caused by a positive AI-ECG result, but participants will be counseled regarding the implications of these results at the time of consent.

As with all research, there is a chance that confidentiality could be compromised; however, we will take precautions to minimize this risk.

- Each participant will be given a study ID which will be recorded and maintained in a secure place at the study site.
- Sequential numbers will be assigned to each study ID which will be used for enrollment de-identification on the AliveCor recordings.
- Acquired data from AliveCor devices will be stored on HIPAA-compliant, encrypted servers.
- Other recorded data will be kept in a secure file on a computer with password protection. Any data recorded on paper documents will be kept behind two locked doors
- Only those personnel involved in data recording and interpretation will be allowed access to data including principal investigator, co-investigators, and other study staff.

Participants will receive the results of the AI-ECG algorithm. The definitive implications of such predictions are not yet known. Both those with positive and negative results will receive information encouraging them to review the results and discuss undergoing cardiac screening with their primary care provider.

This study will utilize AI. The risks associated with this technology and the relevance to this study are outlined in Appendix 10.1.

7.7.2 Known Potential Benefits

The direct benefit to participants in this study may include earlier detection of DCM or other heart conditions. However, study participants may not receive any other direct benefit from participating in this study. The results of this study could potentially lead to a positive paradigm shift in the field of cardiac screening by provision of at-home cardiac screening tools that may support the remote use of AI technology to improve, preempt, and prevent cardiovascular disease.

8 CLINICAL MONITORING

8.1 Clinical Monitoring

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Monitoring for this study may be performed by the Research Institute and will include a random review of certain data.

Authorized representatives of the MC IRB for Mayo Clinic and LGH IRB for LGH may inspect all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records. These two sites will have separate IRB submissions so the expectations are that each site track medical records and site specific documents.

8.1.1 *Data Handling and Record Keeping*

8.1.1.1 *Data Collection and Management Responsibilities*

As with all research, there is a chance that confidentiality could be compromised; however, we will take significant precautions to minimize this risk.

- MC and LGH will maintain its own confidential screening log.
- Digital ECG data transmitted via KardiaRx and KardiaStation will be assigned a study ID. The KardiaRx app can only be used when inputting a 12-character connection code that will be uniquely assigned to each study ID. The data will be transmitted to AliveCor's secure cloud.
- Confidentiality of participant information will be maintained by assigning study identifiers to the medical data. A data set with only the participants' study ID will be shared with Mayo Clinic, for validation of LVEF and other algorithms developed.

Additional Considerations: The following is a list of study participant confidentiality safeguards:

- Data flow procedures – Data identifying participants will be stored in password encrypted files and within REDCap database at Mayo Clinic and LGH separately.
 - Electronic files – Data identifying participants that are stored electronically will be maintained in an encrypted form or in a separate file with device password protection.
 - Forms – Forms or pages containing personal identifying information will be separated from other pages of the data forms and retained in a secure location.
 - Data listings – Participant name, study ID, hospital chart, record number, Social Security Number, or other unique identifiers will not be included in any published data listing.
-

- Data distribution – Data listings that contain participant name, Study ID, or other identifiers easily associated with a specific participant will not be distributed.
- Data disposal – Computer listings that contain participant-identifying information will be disposed of in an appropriate manner.
- Access – Participant records will not be accessible to persons outside the study without the express written consent of the participant.
- Storage – Study forms and related documents retained both during and after study completion will be stored in a secure location.

8.2 Electronic Data Management System

This study will use REDCap for data capture of all study data. Access to the trial in REDCap is granted through the application to all people with the appropriate roles assigned in the delegation log. Data tracking, editing, updating, and reporting will be tracked in REDCap. For statistical analysis, secure data access via the REDCap API will be used to provide the data for the analysis.

8.3 Supporting Documentation

Essential study documents will be collected and stored in participant binders or electronically. Documents include but are not limited to:

- Medical History
- ECG data results from AliveCor
- Health care utilization to support the documentation of engagement of definitive screening, including TTE results if available

8.4 Record Retention

The study team will be responsible for ensuring that all materials contain the Participant study ID, and protocol number. All PHI must be redacted if shared outside the institution. We will ensure that personal information and medical records are kept private. If information from this study is published or presented at scientific meetings, participants name and other personal information will not be used.

The study participants' contact information will be securely stored at the study site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for 6 years as dictated by the HRPP.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the onsite secure servers or in REDCap. The study data entry and study management systems used by the study site and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at LGH Research Institute.

8.4.1 Publication and Data Sharing Policy

This study will comply with the data sharing agreements established between Penn Medicine LGH and AliveCor, Penn Medicine LGH and Central Pennsylvania Clinic, and Penn Medicine LGH and Mayo Clinic. Mayo Clinic may utilize the de-identified AI-ECG data for algorithm optimization.

8.4.2 Conflict of Interest Policy

Research investigators and personnel are required to disclose any financial interests related to their job responsibilities on an annual basis. Financial interests are reviewed by the Research Compliance Committee as protocols are submitted and as they come up for continuing review. Any potential conflicts of interest must be managed to the satisfaction of the IRB to minimize influence on participant safety and study integrity.

8.5 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Informed consent will be IRB-approved, and the participant will be asked to read and review the documents. The study team/PI will explain the research study to the proband and FDR either at a Mayo Clinic or over the phone, at LG Health practice or over the phone. A provider will not be required to obtain informed consent but may aid in explaining the study to the participant. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as a research participant.

Potential participants will have the opportunity to carefully review the written consent form and ask questions. The potential participants should have the opportunity to consider the consent prior to agreeing to participate. Study staff will answer any questions that arise and be present to review the documents in a private room or over the phone. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the consent form will be given to the participant electronically or as a hard copy for their records. The informed consent process will be conducted and documented in REDCap prior to study-specific activities.

8.6 Funding Source

Funding for this study will be provided for LGH through a grant from the Louise von Hess Foundation. Funding for this study at Mayo Clinic will be provided by the department of Cardiology.

8.7 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale

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10 APPENDIX

10.1 Artificial Intelligence (AI) Assessment Risk

Artificial intelligence involves the engineering of intelligent machines which have the capability to learn and self-modify algorithms based on experience (new data). These programs have the ability to detect information and associations which are subliminal to ordinary human senses and comprehension thus allowing the deduction of conclusions which seem unintuitive or even magical. The implications for medicine are exciting and will likely improve the diagnosis and treatment of many common as well as unusual diseases.

There is legitimate concern about the impact of artificial intelligence/machine learning (AI/ML) in the medical setting. Among these considerations are:

1. Privacy concerns regarding personal health information (PHI)
2. Accountability for medical decision making
3. Deference to AI/ML algorithms in place of sound medical experience
4. The application of algorithms for which the building data set was deficient or inappropriate.

There are different levels of AI/ML with different associated risks. General AI (AGAI) is able to analyze all types of information and generate conclusions based upon the general fund of historical knowledge. Limited AI is designed to perform pre-specified analysis based upon smaller, constrained data sets and draw more focused conclusions related to narrow, specific questions.

When considering the application of AI/ML to medical research it seems reasonable to assess the risk based upon the specific AI/ML task.

RISK FACTOR ASSESSMENT

1. General (AGI) or limited (specific task) AI
 2. Patient facing
 3. AI software which interfaces with the electronic medical record (EMR) and has access to PHI
 4. AI analysis will be used for patient management
 5. AI algorithm is cloud based (not incorporated into the EMR)
 6. Limited provider access (password protected) to AI software
 7. Limited access to AI software and analytic results (open or closed access)
 8. Specific (password protected) provider/investigator access to AI analyzed data results
 9. Limited data input for AI analysis
 10. Is PHI de-identified or anonymized and if yes, is the process checked for data security and by whom
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Table 1: Significance of AI derived information input to healthcare decision making (modified)
(1)

State of health care situation	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	IV
Serious	III	II	I
Non-serious	II	I	I

The characteristics of the clinical situation also impacts the specific risk profile. Considerations would include urgency of the situation, the level of patient risk and impact of the proposed intervention.

To help simplify and clarify the risk assessment of AI related research trials and assure patient safety while facilitating this new avenue of research the following strategy is proposed.

Protocols would undergo a risk assessment and require a specific response to each of the proposed questions. Trials with limited risk (none or few positive risk factors) in a stable medical scenario could undergo local IRB review. Protocols involving multiple risk factors and/or utilized in a more critical situation would require more intense review and supervision. Such protocols might require an outside IRB review depending upon the expertise of the local institution. Subsequent monitoring would be more intensive with regular ongoing audits.

The goal of this proposal is to enhance the safety of AI related research while not placing burdensome regulations on study development or investigators.

The FDA has determined that AI should be regulated as a medical device. As such the principle of significant or non-significant risk would apply. Significant risk means that an investigational device (2):

1. Is intended as an implant and presents a potential for serious risk for health, safety or welfare of a participant.
2. Is to be used for supporting or sustaining life
3. Is for use of substantial importance in diagnosing, curing, mitigating or treating disease
4. Otherwise presents a potential for serious patient risk

Non-significant risk includes devices that are:

1. Noninvasive
2. Does not require invasive sampling

3. Does not introduce energy into a participant
4. Is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

AI In the case of our proposed study; Artificial intelligence electrocardiogram enabled mobile device in screening families for dilated cardiomyopathy (DCM-DETECT Trial) would qualify as a non-significant risk study participant to local IRB regulations (3). None of the risk assessment listed above suggest risk. The health care decision making determination is level 1.

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