Ancillary Study Proposal Form

Atherosclerosis Risk in Communities (ARIC)

Part A: Basic Study Information and Projected Impact on ARIC

1. **Title of study:** AI-based cardiac CT reading for predicting CVD risk in the 75-and-older population

2. **Principal investigator(s)** (name, institution, address, phone, e-mail address):
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3. **List collaborators with email addresses** (must include the name of at least one ARIC investigator who will serve as the sponsor and has reviewed and approved this proposal):

Name of ARIC sponsor: The co-PIs are ARIC investigators

Date of approval of this proposal by ARIC sponsor: N/A

Funding source (institute and grant mechanism) and date of grant submission (if applicable): NHLBI, July 2024

Proposed starting and ending dates: from April, 2025 to March, 2029

Collaborators: Matthew Budoff (mbudoff@lundquist.org***), Sadeer AI-Kindi (***sal-kindi@houstonmethodist.org***), Amil Shah (***Amil.Shah@UTSouthwestern.edu***), Yejin Mok (***ymok2@jhu.edu***)***

4. Participant Burden Classification (select one)

a. Data analysis only (including pooling projects/meta-analysis) ☒ ***Already collected CT images and medical charts will be used. So, there is no contact with participants and no consumption of stored specimens.***
b. Laboratory/biospecimen use only ☐

c. Participant contact but NO laboratory/biospecimen collection or use ☐
d. Participant contact with laboratory/biospecimen collection or use ☐

If you selected (b), please briefly summarize biospecimen type, location, and availability. If you are uncertain about sample availability, please work with your sponsor and/or contact ARIC investigators before proceeding:

5. Coordinating Center Involvement ☒ Yes ☐ No

6. Brief Summary of Proposed Research and Projected Impact on the ARIC Study (<100 words)

This is a renewal of R01 "Quantifying cardiovascular calcification at very old age for personalized risk classification" (the original ARIC AS #2016.06), which conducted non-contrast CT in ~2,300 ARIC participants aged 75+. This renewal will expand the original grant in three areas: 1. AI-based cardiac CT readings; 2. CT readings beyond vascular/valvular calcification, and 3. Detailed phenotyping of CVD outcomes (type 1 and type 2 MI). The new information from additional CT readings (e.g., pericardial fat) and MI subtype classification from this ancillary study will be useful for the ARIC community beyond this ancillary study.

7. **Summary of ARIC centers and tasks involved** – Leave cell blank if Not Applicable

Center	Enroll or examine participants (N)	Assay samples (N participants)	Provide samples (N participants)	Provide data files (yes/no)	Analyze data (yes/no)
Forsyth Co. Field Center				***No***	***No***
Jackson Field Center				***No***	***No***
Minnesota Field Center				***No***	***No***
Washington Co. Field Center				***No***	***No***
DNA Central Lab					
MN Chem Lab					
Lipid Central Lab					
ECG Reading Center					
Coordinating Center (UNC)				***Yes (PDF of medical charts collected for MI adjudication among participants who underwent CT at visit 7)***	***No***
Other (specify) ***UCLA CT Reading Center (Matthew Budoff)***				***Yes (new readings and sharing CT images with Houston Methodist)***	***No***
Houston Methodist DeBakey Heart & Vascular Center (Sadeer AI-Kindi)				***Yes (will conduct AI readings of cardiac CT images)***	***Yes***

8. IRB

Select the IRB plan for this ancillary study (either sIRB or Local IRB) and the reason(s) for selection:

sIRB ☐

a. new data collection at more than one center either directly with ARIC participants or using medical records ☐

b. lab analysis of ARIC stored samples that use identifiers or require reporting data back to participants ☐

c. more than one center will see PHI for the study ☐

d. there eventually may be an FDA application ☐

or

Local IRB ☒

a. proposals that only use only existing ARIC deidentified data (e.g., most student projects, career development projects) will qualify as exempt or non-human subjects research ☒

b. exclusively single center proposals (this can include some investigators at other sites who are only coauthors or provide services but never see participants or PHI ☐

c. lab studies where the ARIC component is already approved in the sIRB parent protocol ☐

9. ARIC participant and staff involvement

a. ARIC Field Centers:
Describe effort (and estimated time) required of ARIC staff at each participating center. Include consent, collection of samples, etc. ***N/A***

b. Describe participant involvement.
Describe number of subjects needed; special characteristics of study population; age and sex distribution. Will participants be contacted, interviewed, examined, or asked to provide specimens? Will this contact be embedded into an existing clinic visit or involve a separate (de novo) visit? Will the study involve radiation or administration of a drug or contrast? ***N/A***

d. Estimate time required of each participant. ***N/A***

e. Describe any human subject protections issues including level of risk to participants and protections against risk. ***We will share already collected CT images with the Houston Methodist DeBakey Heart & Vascular Center (Dr. Sadeer AI-Kindi) and PDF files for MI subtype classification with the Exact Myocardial Injury Adjudication Group (EMIAG) (Dr. Andrew DeFilippis). See section #13 below regarding more details about***

EMIAG. However, CT images and PDF files do not contain any personally identifiable information.

10. Describe ARIC Coordinating Center involvement

** Unless you provide strong justification, the Coordinating Center must be included, and its costs budgeted.*

If activities will be performed at the Coordinating Center, support for these activities should be included in the grant application. Guidelines for reimbursement are provided on the ARIC website.

Describe effort (and estimated time) required of ARIC Coordinating Center staff. Specifically:

a. Will the Coordinating Center be involved in data collection, tracking, or preparation of forms or software? or will these tasks be completed locally by the Ancillary Study, and a data file sent to the Coordinating Center? ***There are two main activities of the Coordinating Center (CC) for this ancillary study: 1. Organizing new variables created from the project (additional readings of existing cardiac CT images and MI subtypes [e.g., type 1 and type 2 MI]) and 2. Sharing PDF files for MI adjudication (whatever CC has collected as their routine) with the investigators of this ancillary study.***

b. If a Reading Center or laboratory is involved, will data be sent directly from the Reading Center or laboratory to the Coordinating Center for processing, or will processing be done locally (either by the Ancillary Study or at the Reading Center/Laboratory)? ***N/A***

c. Will analyses be done locally by the Ancillary Study or by analysts at the Coordinating Center? If analyses will be done locally, should Coordinating Center verify the analyses? ***The analyses will be done locally. The Coordinating Center does not need to verify the analyses.***

11. Stored ARIC specimens

If stored specimens will be requested from the ARIC Laboratories, support for these activities should be included in the grant application. If the Ancillary Study is approved, please contact the appropriate lab for estimates and budgeting requirements.

Describe materials to be used (e.g., stored plasma, urine, DNA). If blood samples are requested, please review the Criteria for Approval section of the Ancillary Study Policy (https://sites.cscc.unc.edu/aric/ancillary-studies-pfg) in consideration of your description of the following:

Study participants and material requested: ***N/A***

Yes/No	Cohort	Total Number of Specimens	Full Cohort (or→)	Number of Cases	Number of Controls
	All parent study participants (or ↓)				
	Specify sample and specimens in each sample/stratum				

Type of Specimen	N	Volume Requested	Time point (e.g. visit*)	Specify proposed lab and analytes to be assayed at catch lab (be specific)
Serum		ul		
EDTA plasma		ul		
Citrate plasma		ul		
DNA		ug/ng		
Urine		ul		
Other (specify)				

* Please contact ARIC in advance and indicate here how many tubes of each visit and type you are requesting:

a. Is the proposed work consistent with the stipulations in the ARIC informed consent form? ☐ Yes ☐ No (The informed consent forms can be obtained from the collaborating ARIC investigator).

b. Are thawed/re-frozen acceptable? ☐ Yes ☐ No

If No, specify reasons for specific assays:

c. Describe efforts to integrate sample needs with those of other studies to conserve sample and/or limit freeze-thaw cycles.

d. If approved, when will samples be requested for retrieval?

12. Genomic information (defined as any data from a participant's DNA):

a. Does your proposal include any genomic materials? (please check one)
☒ No (go to question 13) ☐ Yes

b. Name the gene(s), genotypes, SNPs to be investigated:

c. Is genetic information used to address a primary aim or secondary aim of ARIC? (please check one or both)

☐ Primary aim (heart/vascular disease)
☐ Secondary aim (other health conditions)
List the conditions addressed:

d. Should DNA-based results be reported to patients' physicians? Base your response on your knowledge of existing literature and current practice regarding increased risk and availability of treatment for adverse outcomes associated with the gene mutations to be studied.

13. Does this study involve the support or collaboration of a for-profit corporation, or do you intend to use the data to patent any process, aspect or outcome of the analysis? ***The Exact Myocardial Injury Adjudication Group (EMIAG) core laboratory will provide comprehensive myocardial injury case assessment and MI subtype adjudication. EMIAG is adjudicating MI subtypes for MESA through an R01 (R01 HL158976). Dr. Andrew DeFilippis, Medical Director of the Cardiovascular Intensive Care Unit, Associate Professor of Medicine, Vanderbilt University Medical Center, is the lead of EMIAG.***

14. What is the advantage, both to ARIC and yourself, of conducting the study within the ARIC cohort versus another population? ***The new information from additional CT readings (e.g., pericardial fat) and MI subtype classification from this ancillary study will be useful for the ARIC community beyond this ancillary study. Leveraging existing CT images, the investigators can explore their aims efficiently.***

15. Discuss impact on and coordination with ongoing ARIC studies (main study or other Ancillary Studies): ***We do not anticipate any negative impact since we will use already obtained CT images and PDF files for MI adjudication. Also, as noted above, the availability of comprehensive information from CT scans and adjudicated type 1 and type2 MI data will positively impact the ARIC community.***

16. Provide the following assurances (answer each):

a. Who (name and position) will report progress of the study in the fall of each year? (Ancillary Study PI or designate preferred) ***Kunihiro Matsushita***

b. How will confidentiality of ARIC participants be maintained? ***This ancillary study will follow the same procedure used in ARIC in this regard.***

c. Data collected by the Ancillary Study, will be provided to the ARIC Coordinating Center for integration into the main database. This will include documentation of newly collected data with labels, and/or laboratory results as well as documentation on methods, visits and units used with specific instructions for using the data in analyses. such as exclusions that were applied. After that has been done the Ancillary Study investigators will receive the integrated file containing data from the main study.

The Ancillary Study PI will be given the first and exclusive opportunity to analyze, present and publish data collected under the auspices of the Ancillary Study. After a reasonable time (in general, 12 months after data cleaning is complete or 12 months after acceptance of primary manuscript, whichever is earlier), Ancillary Study data will be made available for additional uses by other ARIC investigators. It is the responsibility of the Ancillary Study PI to state in writing to the ARIC Steering Committee any special circumstances that would warrant an exception to these guidelines for data sharing. In the spirit of encouraging collaboration, reasonable and justified requests for limiting Steering Committee access to the data will be honored, or a compromise will be worked out. ***Noted.***

d. Will the Coordinating Center be receiving data from your ancillary study? ***We will share new information from the additional CT readings and MI subtype adjudications with CC.***

e. How many papers do you estimate will be written from the Ancillary Study? ***>10***

f. Variables/measurements from the ARIC main study database to be analyzed: ***The variables of interest from the main ARIC study will include age, sex, race, body mass index, blood pressure, hypertension medication, diabetes, lipids, lipid-lowering medication use, history of cardiovascular disease (coronary heart disease, stroke, and heart failure), physical activity, physical function, self-rated health, echo parameters.***

17. If the study will have clinical implications, explain and describe the plan for reporting results to participants and providing recommendations for follow up:
The additional CT readings in this ancillary study are not yet established as clinical routine care. Thus, we are not planning to report any information to participants. Regarding the classification of MI subtypes, it is likely that relevant participants already received relevant information from their providers. Even if not, providing that subtype information from the past would not benefit medical care for our participants.

Part B Abbreviated Ancillary Study Proposal

Please provide a brief (2 to 4 page) description of the proposed study. Include the following:

Purpose/Aims:

Aim 1: To evaluate AI-based coronary "calcium-omics" vs. manual Agatston score for their associations with detailed phenotypes of ASCVD (type 1 MI, type 2 MI, and ischemic stroke)

Aim 2: To assess AI-based CT reading of cardiac chamber size and pericardial fat vs. corresponding manual CT reading vs. echo-based chamber size for their associations with heart failure (HF), including HF with preserved ejection fraction (HFpEF) and reduced EF (HFrEF)

Aim 3: To examine AI-based cardiac CT readings for predicting total CVD (ASCVD and HF) in the 75-and-older population

Background:

As adults age to 75 years and older, attention to cardiovascular disease (CVD) expands beyond traditional outcomes like type 1 myocardial infarction (MI) and heart failure with reduced ejection fraction (HFrEF) to the preponderant age-related outcomes of type 2 MI and HF with preserved ejection fraction (HFpEF).[1] While non-contrast cardiac-gated computed tomography (CT) for coronary artery calcium (CAC) is well established for predicting the former outcomes throughout middle age,[2] there is less research on leveraging the entirety of information in these CT scans for prediction of the most common CVD outcomes in adults aged 75 and older.[3]

Indeed, we are in the midst of a revolution in the way we use imaging data to acquire actionable clinical information, made possible by advancements in artificial intelligence (AI). For example, the field of radiomics has revealed new patterns in CT images that carry substantial prognostic information, as evidenced by extensive preliminary data on coronary "calcium-omics" and the prediction of coronary events.[4] AI also allows the rapid interpretation of non-coronary findings on cardiac CT scans that heretofore were too laborious to measure to provide clinical value. For example, our proposal of automated quantification of cardiac chamber size, pulmonary artery size, and pericardial fat may allow rapid and comprehensive risk prediction of HFpEF.

There is an urgent need to study AI-based cardiac CT interpretation in the age >75 population, as most prior studies have excluded this rapidly growing age group (mean ages of prior studies ranging from 50-65 years). This is a critical gap since the 75-and-older population is more likely to have calcification in surrounding structures (e.g., mitral annulus, heart valves, and the aorta), which may interfere with the accuracy of automated AI reading. Also, relevant parameters can differ across CVD outcomes (e.g., type 1 vs. type 2 MI).

This application is a renewal of our successful R01 "Quantifying cardiovascular calcification at very old age for personalized risk classification" (R01HL136592), which conducted non-contrast cardiac CT with Core lab-based manual quantification of CAC and extra-coronary calcification (ECC [e.g., cardiac valves and thoracic aorta]) in ~2,300 participants age 75+ from the Atherosclerosis Risk in Communities (ARIC) study at visit 7 (2018-19). The emphasis in our prior R01 was on the prediction of atherosclerotic CVD (ASCVD) without differentiating type 1 vs. type 2 MI. The renewal will extend the original project in the following three domains: 1. AI-enabled cardiac CT reading; 2. Expanding CT

reading beyond vascular/valvular calcification; and 3. Detailed phenotyping of CVD outcomes (type 1 MI, type 2 MI, HFpEF and HFrEF).

Hypotheses:
H1: AI-based "calcium-omics" (comprehensive assessment of shape, density, volume, number of calcifications, and more) will be more strongly associated with ASCVD than the traditional Agatston score. We will also be able to identify unique calcification predictors for each of type 1 MI vs. type 2 MI, with pathophysiological implications.

H2: AI-based comprehensive reading of the size of both atriums, both ventricles, pulmonary artery, and pericardial fat will be similarly or more strongly associated with HF compared to the corresponding manual CT reading and echo-based cardiac chamber sizes (often challenging to quantify right atriums and ventricles). This aim will also examine the potential etiological contributions of pericardial fat to HFpEF vs. HFrEF.

H3: AI-based cardiac CT reading alone will predict total CVD similarly or even better than the set of traditional predictors (e.g., age, sex, blood pressure, diabetes), and the best prediction will be obtained by combining AI reading and traditional predictors. We will develop and validate a CVD risk prediction tool with AI-based cardiac CT readings for the 75-and-older population.

Experimental Design (include sample size justification):

Study population: *At ARIC visit 7, ~2,300 participants underwent non-contrast cardiac-gated CT scanning (73% of the eligible participants). This renewal will include all participants with cardiac CT data at visit 7 and conduct additional readings of already acquired cardiac CT images.*

Manual CT reading of chamber size and pericardial fat*: The reading center of ARICAC at UCLA (Dr. Matthew Budoff) has established approaches to quantify cardiac chamber size and pericardial fat. Details have been published previously.*[5-8]

AI reading of coronary "calcium-omics", chamber size, and pericardial fat: *Coronary "calcium-omics" indicates an AI-based comprehensive assessment of shape, density, volume, number of calcifications, and territorial features (e.g., volume score in left anterior descending artery, number of lesions in right coronary artery, and distance from top to last lesion in left circumflex). Dr. Sadeer Al-Kindi at Houston Methodist, a co-I of this ancillary study, will lead AI-based readings including coronary calcium-omics, chamber size, and pericardial fat. Detailed methods have been published previously.*[4, 9]

MI adjudication: *As described above, the Exact Myocardial Injury Adjudication Group (EMIAG led by Dr. Andrew DeFilippis) core laboratory will provide comprehensive myocardial injury case assessment and MI subtype adjudication. EMIAG will use the same adjudication of MI subtypes used in MESA. Although details were published elsewhere,*[10] *the process includes a minimum of two independent physician reviews of each case which will include collection of pertinent case characteristics essential to identifying, differentiating, and characterizing all the*

myocardial injury types (including MI type 1-5) as defined in the Fourth Universal Definition of MI.[11]

Analytic plan:

Aim 1:

Among variables quantified as part of "calcium-omics," we will eliminate irrelevant or highly correlated features using the univariate Cox model. We will select the most informative and non-correlated features using LASSO with 10-fold cross-validation. These features will be aggregated into a single "calcium-omics" score by summing the products of these features by their corresponding coefficient (i.e., "risk score" = the sum of xβs). Then, we will use multivariable Cox models to compare "calcium-omics" and Agatston score regarding their associations with ASCVD, independently of traditional risk factors (i.e., age, sex, blood pressure, antihypertensive medication use, total and HDL cholesterols, lipid-lowering medication use, diabetes, and smoking status). Agatston score will be categorized into 4 groups: 0-99, 100-299, 300-999, and ≥1000, and to make a fair comparison, we will categorize calcium-omics score using the same percentiles corresponding to the aforementioned Agatston categories, and compare hazard ratios across these categories. We will also compare c-statistics based on "calcium-omics" score vs. Agatston score. We will repeat the analysis for type 1 MI vs. type 2 MI, separately.

Aim 2:

We will first assess the correlation between AI-based chamber size, manual CT chamber size, and echo-based chamber size for each of left atrium, left ventricle, right atrium, and right ventricle. Subsequently, we will use Cox models to examine the association of each chamber size indexed to height$^{2.7}$ with HF and different types of HF, namely HFrEF and HFpEF. For the comparison across modalities, we will categorize each chamber size by quartiles and compare hazard ratios for Q4 vs. Q1 as well as c-statistics. Seemingly unrelated estimations will be used to formally compare hazard ratios for HFrEF vs. HFpEF.

Aim 3:

As in Aim 1, we will select the most informative and non-correlated features using LASSO with 10-fold cross-validation for total CVD (ASCVD and HF) using Cox proportional hazards models. Here, we are interested in total CVD since this is the outcome used in the new American Heart Association PREVENT® CVD risk score.[12] *Once we identify AI-based cardiac CT predictors, we will evaluate c-statistics and calibration and compare those based on traditional risk factors. We hypothesize that a set of AI-based cardiac CT predictors will predict total CVD better than traditional risk factors in the 75-and-older population. We will assess whether any traditional risk factors can improve the prediction of total CVD beyond AI-based cardiac CT predictors. If that is the case, we will develop a risk prediction model combining AI-based cardiac CT predictors and some traditional risk factors. We will externally validate this riks prediction model using data from MESA participants aged 75 or older at visit 5 (n~700).*

Methods, including:

Participant involvement (if any): ***N/A***

Data to be collected by the ancillary study (attach questionnaires and forms): ***We will only use already abstracted cardiac CT assessment or collected medical charts for MI adjudication.***
Analysis Methods: ***See the section of "Experimental Design" above.***

Literature References

1. Baron T, Hambraeus K, Sundström J, Erlinge D, Jernberg T and Lindahl B. Type 2 myocardial infarction in clinical practice. *Heart*. 2015;101:101-6.
2. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC, Taylor AJ, Weintraub WS and Wenger NK. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults: Executive Summary. *Journal of the American College of Cardiology*. 2010;56:2182-2199.
3. Wang FM, Cainzos-Achirica M, Ballew SH, Coresh J, Folsom AR, Howard CM, Post WS, Wagenknecht LE, Budoff MJ, Blaha MJ and Matsushita K. Defining Demographic-specific Coronary Artery Calcium Percentiles in the Population Aged ≥75: The ARIC Study and MESA. *Circ Cardiovasc Imaging*. 2023;16:e015145.
4. Hoori A, Al-Kindi S, Hu T, Song Y, Wu H, Lee J, Tashtish N, Fu P, Gilkeson R, Ra-Jagopalan S and Wilson DL. Enhancing cardiovascular risk prediction through AI-enabled calcium-omics. *ArXiv*. 2023.
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6. Budoff MJ, Mao S, Wang S, Bakhsheshi H and Brundage BH. Simple single-section method for measurement of left and right atrial volumes with electron-beam CT. *Acad Radiol*. 1999;6:481-6.
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9. Hu T, Freeze J, Singh P, Kim J, Song Y, Wu H, Lee J, Al-Kindi S, Rajagopalan S, Wilson DL and Hoori A. AI prediction of cardiovascular events using opportunistic epicardial adipose tissue assessments from CT calcium score. *ArXiv*. 2024.
10. DeFilippis AP, Lidani KCF, Nam Y, Trainor PJ, Johnson WC, Heckbert SR, McClelland RL, Blaha MJ and Nasir K. Risk factor associations with individual myocardial infarction subtypes and acute non-ischemic myocardial injury in the Multi-Ethnic Study of Atherosclerosis (MESA): Design and rationale. *Am Heart J*. 2023;260:151-173.
11. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA and White HD. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation*. 2018;138:e618-e651.
12. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, Blaha MJ, Carson AP, Chang AR, Ciemins E, Go AS, Gutierrez OM, Hwang SJ, Jassal SK, Kovesdy CP,

Lloyd-Jones DM, Shlipak MG, Palaniappan LP, Sperling L, Virani SS, Tuttle K, Neeland IJ, Chow SL, Rangaswami J, Pencina MJ, Ndumele CE and Coresh J. Development and Validation of the American Heart Association's PREVENT Equations. *Circulation*. 2024;149:430-449.

Please send the completed form to ARIC-AS@unc.edu and use 'ARIC ancillary proposal' in the subject line