Ancillary Study Proposal Form

Atherosclerosis Risk in Communities (ARIC)

I. Basic Study Information and Projected Impact on ARIC

1. Title of study: ***Quantifying cardiovascular calcification at very old age for personalized risk classification***

2. Principal investigator(s) (name, address, phone and fax numbers, e-mail address): ***Kunihiro Matsushita: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology, and Clinical Research, 2024 E. Monument St., Suite 2-600, Baltimore, MD 21287, Tel (443) 287-8766 Fax (443) 683-8358, kmatsush@jhsph.edu and Michael Blaha: Department of Cardiology, The Johns Hopkins Hospital, Blalock 524D1, 600 N Wolfe St, Baltimore, MD 21287, mblaha1@jhmi.edu.***

3. Collaborators (must include at least one ARIC investigator): ***Josef Coresh, Matthew Budoff, and Aaron Folsom***

4. 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)	Analyze data (yes/no)
Forsyth Co. Field Center	***~860***			
Jackson Field Center	***~850***			
Minnesota Field Center	***~1150***			
Washington Co. Field Center	***~1070***			
DNA Central Lab				
MN Chem Lab				
Lipid Central Lab				
Hemostasis Central Lab				
ECG Reading Center				
Coordinating Center (UNC)				
Other (specify)				

5. ARIC participant and staff involvement:

A. Participants:
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 the study involve radiation or administration of a drug or contrast? If so, describe participant involvement. Estimate time required of each participant.
Note that contacts with participants must be done in cooperation with field centers and all contacts must be recorded in the coordinating center's data system for tracking phone calls and contacts. The latter requires data management updates by the ARIC coordinating center, to be reimbursed by the ancillary study. ***This proposal is designed to perform non-contrasted cardiac-gated chest computed tomography (CT) to assess coronary artery calcification (CAC) as well as extra-coronary calcium (ECC) (i.e., aortic and mitral valves and thoracic aorta) during the ARIC visit 6 (under NCS) and visit 7 (under contract). Of importance, there would not be extra radiation to assess ECC, and we anticipate ~1 mSv of radiation for each participant.[1] For reference, the average yearly background radiation dose (primarily from radon gas in the home) is around 3 mSv.[2] We are aiming to include visit 6 ARIC participants from May 1 2017 onward and all visit 7 participants (total of ~3,900 participants from the four field centers). However, participants will be able to opt in/out from this study independently of the ARIC NCS and main ARIC visit. Some ARIC participants at the Jackson field center underwent CAC scan in the Jackson Heart Study and the GENOA. Dr. Matsushita is now collaborating with Drs. Mosley and Griswold to learn more details, and a coordination (e.g., not inviting those who had CAC in the last five years) will be made accordingly. The scan time is expected to be less than 5-10 min. Accounting for the time to obtain informed consent and transfer participants to CT facilities from the field centers, we estimate the total required time for each participant to be 30-45 min.***

B. Stored ARIC specimens:
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 (http://www2.cscc.unc.edu/aric/sites/default/files/public/listings/Ancillary%20StudiesPolicy%20NEW%2017Feb2014.pdf) in consideration of your description of the following:

1. Study participants and material requested:

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

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	***N/A***	
EDTA plasma		ul	***N/A***	
Citrate plasma		ul	***N/A***	
DNA		ug/ng	***N/A***	
Urine		ul	***N/A***	
Other (specify)				

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

2. 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). ***N/A***

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

   If No, specify reasons for specific assays: ***N/A***

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

5. If approved, when will samples be requested for retrieval? ***N/A***

C. ARIC Field Centers:
Describe effort (and estimated time) required of ARIC staff at each participating center. Include consent, collection of samples, etc.
Total estimated time: 30-45 min
Informed consent: 10 min
Transfer to CT facility: 5-10 min
CT preparation: 5-10 min
Scan time: 5-10 min

D. ARIC Coordinating Center:
Describe effort (and estimated time) required of ARIC Coordinating Center staff. Specifically: ***Data linkage, quality control, and data distribution for variables created in this ancillary study. We will compensate $~35,000 per year to the Coordinating Center for these activities (details will be determined through the conversation with Dr. David Couper).***

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

i. 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? ***The Coordinating Center will assist with creating recruitment/consent forms. Also, CAC and ECC data collected at each field center will be transferred to the Coordinating Center, and then will be distributed to each field center.***

ii. 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)? ***Research readings of CAC and ECC will be performed at the Los Angeles Biomedical Research Institute (led by Matthew Budoff, co-investigator of this project) and all study data will be sent to the Coordinating Center.***

iii. 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? ***Data analyses will be done locally at Johns Hopkins University. There is no need for analysis verification by the Coordinating Center.***

6. 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 7) ☐ Yes (see question 6B)

   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.

7. Proposed starting and ending dates: ***April 1, 2017-March 31, 2022***

8. Estimated cost by year; number of years: ***$500,000 per year for 5 years.***

9. Source of funding; date of submission: ***National Heart Lung and Blood Institute R01 (June 5, 2016)***

10. 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? ***N/A***

11. What is the advantage, both to ARIC and yourself, of conducting the study within the ARIC cohort versus another population? ***CAC is established as one of the most potent predictors of atherosclerotic cardiovascular diseases and recommended when cardiovascular risk prediction needs to be refined beyond the assessment of traditional risk factors in those aged 40-75 years old for clinical decision making.[3,4] Also, recent studies demonstrate that extra-coronary calcium (ECC) (i.e., aortic and mitral valves and thoracic aorta) detected on a routine CAC scan provides prognostic information beyond CAC.[5] However, prognostic data of CAC specifically among contemporary very old adults are surprisingly sparse. Also, using rich data already collected in ARIC from midlife we will be able to identify the major 30-year lifestyle, social, and clinical factors predictive of healthy vascular aging, defined as low and zero CAC and ECC.***

12. Impact on ongoing ARIC studies (main study or other Ancillary Studies): ***We expect our study to have a positive impact on many ongoing or future studies for CVD by providing opportunities to incorporate CAC and ECC data as a potent predictor of CVD risk or another measure of subclinical atherosclerosis.***

13. Provide the following assurances (answer each):

(1) Who (name and position) will report progress of the study in the fall of each year? (Ancillary Study PI or designate preferred) ***Kunihiro Matsushita, MD, PhD, Associate Professor, Johns Hopkins University (Ancillary Study Co-PI)***

(2) How will confidentiality of ARIC participants be maintained? ***The ancillary study researchers with access to the individual data are also ARIC main study researchers. They will follow the usual measures to maintain confidentiality (data maintained in security-protected computers, etc.).***

(3) 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.

(4) How many papers do you estimate will be written from the Ancillary Study? ***5-10 papers***

(5) Variables/measurements from the ARIC main study database to be analyzed: ***Demographic variables, basic clinical parameters such as blood pressure, body weight, height, and laboratory measures like lipids and blood glucose, and clinical history.***

14. If the study will have clinical implications, explain and describe the plan for reporting results to participants and providing recommendations for follow up: ***As a clinically established examination, we are planning to implement local clinical reading and share the report including CAC Agatston Score to participants.***

II. Abbreviated Ancillary Study Proposal

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

Background/Purpose/Aims/Hypotheses: ***Predicted risk is the central component of decision-making in primary prevention of atherosclerotic cardiovascular disease (ASCVD).[3,4,6] However, classifying risk in very old adults (>75 years) remains extremely challenging. Existing risk prediction tools are heavily weighted by age, assigning high risk status and therefore recommending treatment for nearly all older adults. This raises concerns about overmedication, drug-drug interactions, and lack of personalization. Competing risk of mortality and morbidity due to other conditions (e.g., cancer, lung disease, and dementia) is another issue in this population, requiring a fine balance between the prevention of CVD based on accurate risk prediction vs. management of other comorbidities for personalized care. However, it is highly unlikely to achieve such accurate risk prediction by merely assessing traditional cardiovascular risk factors at older ages because this approach fails to provide information on cumulative effects (duration*severity) over lifetime and individuals' susceptibility to risk factors.***

In this context, quantification of coronary artery calcium (CAC) is promising, as it reflects both the cumulative effects of and individual's susceptibility to risk factors. High CAC score is well-known as one of the most potent predictors of high ASCVD risk. Recently, zero CAC has been shown to be useful for "de-risking", identifying individuals who may be less suitable for preventive therapy regardless of the status of traditional risk factors.[7] Recent studies also demonstrate that extra-coronary calcium (ECC) (i.e., aortic and mitral valves and thoracic aorta) detected on a routine CAC scan provides prognostic information beyond CAC.[5]

However, prognostic data of CAC and ECC among very old adults are surprisingly sparse. Thus, we propose to perform non-contrasted cardiac-gated computed tomography among ~3,900 participants aged ≥75 years in the Atherosclerosis Risk in Communities (ARIC) Study during forthcoming visits between 2017 and 2019 and to develop a dedicated CVD risk classification engine incorporating CAC and ECC for very old adults.

To maximize the relevance of our CVD risk classification tool, we will simulate cost-benefit of CAC/ECC-based personalized CVD risk classification in the context of clinical outcomes.

Aim 1: To develop a contemporary risk classification engine for CVD risk for very old adults

Hypothesis 1.1: Traditional risk factors will perform poorly for classifying CVD risk in very old adults, and competing risk models accounting for comorbid illness will improve calibration of CVD.

Hypothesis 1.2: Information on CAC (Agatston score, volume, distribution, and density) will improve classification of CVD risk (particularly CHD), above and beyond traditional risk factors in very old adults.

Hypothesis 1.3: Information on ECC will be useful to better classify CVD risk, particularly stroke and HF risk, above and beyond traditional risk factors and CAC in very old adults.

Aim 2: To assess whether up to 30-y cumulative exposures of other risk factors and markers will provide similar prognostic information as CAC and ECC

Hypothesis 2.1: 30-y cumulative traditional risk factors will provide close but not identical prognostic information to CAC and ECC since they do not account for individual's susceptibility.

Hypothesis 2.2: 27-y cumulative information of cardiac troponin and natriuretic peptide will provide similar prognostic information to CAC and ECC for HF but perform worse for ASCVD (particularly CHD).

Aim 3: To simulate cost-benefit of CAC/ECC-based risk classification in very old adults

Hypothesis 3.1: The incremental cost of CAC/ECC scan is acceptable in light of targeted preventive pharmacotherapy.

Experimental Design (include sample size justification) and Analysis Methods: *CAC and ECC Agatston score, volume, spacial distribution, and density will be quantified at the Reading Center. These variables will be used as predictors in Aims 1 and 2. The CVD risk distribution and reclassification by CAC/ECC-based predicted risk obtained in Aims 1 and 2 will be used as parameters in Aim 3.*

Methods, including:

Participant involvement (if any): ***All eligible participants in ARIC visits 6 and 7 with informed consent will be involved in CT scan.***

Data to be collected by the ancillary study (attach questionnaires and forms): ***As above.***

Literature References

1. Kramer CK, Zinman B, Gross JL, et al. Coronary artery calcium score prediction of all cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. BMJ 2013;346:f1654-f.
2. Radiation Dose in X-Ray and CT Exams. 2015. (Accessed April 4th, 2016, at http://www.radiologyinfo.org/en/info.cfm?pg=safety-xray.)
3. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013.
4. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S1-45.
5. Allison MA, Hsi S, Wassel CL, et al. Calcified atherosclerosis in different vascular beds and the risk of mortality. Arteriosclerosis, thrombosis, and vascular biology 2012;32:140-6.
6. Wolff T, Miller T, Ko S. Aspirin for the Primary Prevention of Cardiovascular Events: An Update of the Evidence for the US Preventive Services Task Force. Rockville (MD)2009.
7. Blaha MJ, Cainzos-Achirica M, Greenland P, et al. Role of Coronary Artery Calcium Score of Zero and Other Negative Risk Markers for Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2016;133:849-58.

Please send an electronic copy of the completed proposal to:
Aaron R. Folsom, M.D. (Principal Investigator) folso001@umn.edu

CC: Nell Malone malone@unc.edu

For Coordinating Center Use Only

Approved? ☐ **Yes** ☐ **No**

Date:

If approved, ancillary study #

May 10, 2016

Dear Kuni,

APPROVAL DECISION

The ARIC steering committee approves your ancillary study, which is assigned ancillary study number 201606. Please refer to this number in future communications.

The committee had the following stipulations:

1. This ancillary study must have an adequate plan and funding to deal with incidental and alert findings on the CT.
2. It must integrate and not interfere with ARIC visit 6 or 7.
3. It needs OSMB approval.

Please read the following expectations about ARIC ancillary studies:

ARIC POLICIES

You must comply with any of the following policies that apply to your study:

- If you are seeking funding, please notify the ARIC coordinating center when you receive the funding or when the ancillary study is not to be initiated due to lack of funding. Also notify the coordinating center when your ancillary study is finished.

- All ancillary studies must file annual reports and eventually share any new data on ARIC subjects with ARIC, as outlined in the ARIC ancillary study policy and NHLBI data sharing policies. In addition, you will need to follow ARIC's manuscript approval policies, as outlined in the ARIC Publication Policies. ARIC study policies can be found at http://www.cscc.unc.edu/aric/.

- If this study involves participant burden, it will need to be approved by the ARIC Observational Study Monitoring Board (OSMB). Please make sure Dr. Wright, the ARIC project officer, has the version of the proposal you want the OSMB to review.

-If this study involves participant burden, contacts with participants must be done in cooperation with field centers and all contacts must be recorded in the coordinating center's data

system for tracking phone calls and contacts. Please contact the coordinating center for further information.

-If this study involves laboratory work, unless exempted, you will need to include blind duplicates identified by the coordinating center in your specimen pool. Please budget funds for the Coordinating Center to draw up the laboratory pull list or to add the appropriate blind duplicates to a list of IDs you provide.

- If you are not affiliated with an ARIC center and require access to data files, or if your study involves biologic samples, you will need to complete a Data and Materials Distribution Agreement (DMDA) available on the ARIC website (Ancillary Studies page), once you obtain funding. Evidence of IRB review for your ancillary study is also required. Please contact Ms. Nell Malone at malone@unc.edu if you need more information.

- If this study involves industry funding, NHLBI will need to review the draft agreement letter between your university and the industry before you (and your school business representative) and company sign the letter. Please contact Dr. Wright to obtain advice and instructions in this regard. Please note that the study cannot start until the agreement letter receives approval by the NHLBI.

BUDGET CONSIDERATIONS

- Please be sure to involve the Coordinating Center in your grant and budget adequate coordinating center costs in your proposal. Please work with Nell Malone malone@unc.edu.

- If this study involves the field centers, please work with the field center PIs as soon as possible to finalize their budgets.

- If this study involves lab samples, please discuss and arrange with the ARIC lab involved the aliquotting, processing, and lab costs.

LETTER FOR GRANT PROPOSAL

A letter for your grant proposal is attached.

Regards,

Aaron R. Folsom, MD

ARIC steering committee chair

COMMENTS, IF ANY, FOLLOW

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May 10, 2016

Kunihiro Matsushita, MD
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E. Monument St., Suite 2-600
Baltimore, MD 21287

Dear Kuni:

I am pleased to convey the approval and enthusiasm of the ARIC steering committee for your ancillary study proposal entitled, "Quantifying cardiovascular calcification at very old age for personalized risk classification." Your project is significant and its topic fits nicely with the aims of ARIC.

By approving this project, ARIC is offering to share its data and resources in order for you to accomplish your aims. In return, of course, you are expected to follow ARIC's ancillary study and publication policies.

We wish you success in this important project.

Sincerely,

Aaron R. Folsom

Aaron R. Folsom, MD
Professor
ARIC Steering Committee Chair