

## ARIC Manuscript Proposal #2467

PC Reviewed: 11/11/14  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

1.a. **Full Title:** External Validation of Jackson Heart Study Prediction Model in ARIC-only African Americans

b. **Abbreviated Title:** Prediction Model Validation in African Americans

### 2. **Writing Group:**

Writing group members:

Name	Contact Information	Responsibilities
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. EF [**please confirm with your initials electronically or in writing**]

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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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### 3. Timeline:

Analysis	November, 2014
Manuscript Writing	November, 2014
Initial Draft	November-December, 2014
Editing- Final Draft	December, 2014
Draft Submitted to P and P Committee	December, 2014
Submission to Journal for Publication	December, 2014

### 4. Rationale:

The JHS has submitted a manuscript on the predictive model for CVD events in African Americans to JAMA. There was an initial favorable review however there is a request by JAMA reviewers for external validation in the ARIC-only African American cohort.

Compared to non-Hispanic whites, African Americans have a higher risk of myocardial infarction<sup>1</sup> and congestive heart failure (CHF),<sup>2;3</sup> and a 2-fold risk of stroke<sup>1</sup> and peripheral arterial disease<sup>4</sup>. Limited studies suggest that the higher risk of CVD in African Americans is directly related to a greater burden of standard CVD risk factors. African Americans have a great burden of obesity and diabetes, and the highest prevalence of hypertension among all ethnicities world-wide.<sup>1;5;6</sup> These observations are consistent with the lower prevalence of an optimal CVD risk factor profile in African Americans; 70% have no more than 3 of the 7 AHA metrics of ideal CV health, and only 11% have 5 or more metrics.<sup>7</sup> Prediction and prevention of CVD in African Americans is, therefore, a public health priority.

A prediction model for African Americans has been completed in the Jackson Heart Study and reviewed by Journal of the Americans Medical Association (JAMA). Reviewers request external validation in other African American cohorts with a specific request to validate in the ARIC-only African American cohort.

### 5. Main Hypothesis/Study Questions:

We hypothesize that external validation for primary and secondary predictive models generated in the Jackson Heart Study will prove the models are successfully predictive of events in the ARIC-only AA cohort.

**Specific Aim:** To perform an external validation of a prediction model for all CVD events (MI, CHD death, revascularization procedures, stroke, angina and claudication) and model for hard outcome only (MI, CHD death and stroke) in African Americans

**Hypothesis:** Our major hypothesis is that novel biomarkers and subclinical disease measures offer incremental predictive utility over standard CVD risk factors for predicting risk of CVD in African Americans. We also posited that a parsimonious combination of risk factors, few novel biomarkers and select subclinical disease measures will offer an efficient approach to CVD risk prediction in this group

**6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

For the validation in ARIC, participants will be eligible if they attended the Examination 3 and had available data on key covariates considered for one or all of the following 3 models to be tested: 1) model using traditional risk factors a widely clinically available model that combines traditional risk factors, ABI and BNP.

**Model 1** (traditional risk factors only): Age, male sex, Systolic BP, Antihypertensive therapy, Diabetes, Total: HDL ratio, eGFR and smoking

**Model 2** (simplified combined model): Age, male sex, Systolic BP, Antihypertensive therapy, Diabetes, Total: HDL ratio, eGFR and smoking, BNP and ABI

For the predictive model to be tested, incidence of a CVD event was defined as the first occurrence of any of four major CVD outcomes (myocardial infarction, fatal coronary heart disease [CHD], congestive heart failure and stroke) or any of the two non-major outcomes (incident angina or intermittent claudication) between date of the visit to a median follow up of 10 years.

Reviewers request additional analysis that allows for comparability with the ACC/AHA Risk Calculator. Therefore reviewers request for authors to perform analysis using only hard outcomes (MI, death from CHD and stroke), participants between 40-79 years old and exclude those on statins. There will be a request for this model to be validated as well in ARIC-only African Americans.

**Statistical Analysis:** In our efforts to ensure generalizability of our predictive models, we propose to perform external validation of our estimated models using data on African Americans in ARIC and MESA cohorts (Justice AC et al. 1999; Steyerberg et al. 2010). We shall apply our predictive model to the validation sample and evaluates performance using concordance statistic (C-statistic) and area under the Receiver Operating characteristics (ROC). We shall also perform calibration of the predictive model using goodness of fit statistics (i.e. Homer-Lemeshaw). We shall also explore other performance metrics such net reclassification improvement (NRI), Integrated Discrimination Index (IDI).

**7.a. Will the data be used for non-CVD analysis in this manuscript?**  Yes  
 No

**b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES\_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES\_DNA = "CVD Research" would be used?**  Yes  
 No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

**8.a. Will the DNA data be used in this manuscript?**  
 Yes  No

**8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES\_DNA = "No use/storage DNA"?**  
 Yes  No

**9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.unc.edu/ARIC/search.php>  
 Yes  No

There are several manuscript proposals that utilize pro-BNP in assessing association and risk in separate projects on mortality, heart failure, and stroke. There are no manuscript

proposals that utilize pro-BNP along with a large number of other predictors in a single model. The most related manuscripts are as follows:

MP 1811 Oluleye – cTNT, BNP, CRP and Mortality

MP 2061 Khalid – BNP in obesity and HFpEF

MP 2099 Agarwal – AF, Biomarkers, and Risk of Stroke and Mortality

MP 2142 Ndumele – Obesity, NT proBNP and HF

MP 2295 BNP, Troponin, Hemoglobin, and Sodium in Acute Decompensated HF

**10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?**     Yes     No

**11.b. If yes, is the proposal**

**A. primarily the result of an ancillary study (list number\* 2012.25 Fox - [Validation of Heart Failure Hospitalizations in African Americans with Echocardiography](#))**

**B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)\* \_\_\_\_\_)**

\*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

**12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

### Reference List

- (1) Roger VL, Go AS, Lloyd-Jones DM et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 2012;125:e2-e220.
- (2) Bahrami H, Kronmal R, Bluemke DA et al. Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. *Arch Intern Med* 2008;168:2138-2145.

- (3) Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol* 2008;101:1016-1022.
- (4) Criqui MH, Vargas V, Denenberg JO et al. Ethnicity and peripheral arterial disease: the San Diego Population Study. *Circulation* 2005;112:2703-2707.
- (5) Vital signs: state-specific obesity prevalence among adults --- United States, 2009. *MMWR Morb Mortal Wkly Rep* 2010;59:951-955.
- (6) Hertz RP, Unger AN, Cornell JA, Saunders E. Racial disparities in hypertension prevalence, awareness, and management. *Arch Intern Med* 2005;165:2098-2104.
- (7) Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. *J Am Coll Cardiol* 2011;57:1690-1696.