ARIC Manuscript Proposal #1095

PC Reviewed: 08/30/05	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) Study using a genetic risk score

b. Abbreviated Title (Length 26 characters): Genetic risk score predicts CHD

2. Writing Group: Writing group members: Alanna C. Morrison, Lloyd E. Chambless, Stephen G. Ellis, John P. Kane, Jim Pankow, Lance A. Bare, James J. Devlin, James T. Willerson, Eric Boerwinkle and other ARIC investigators as desired.

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3. Timeline: Analyses will be completed by May 2005. A manuscript will be in preparation by June 2005.

4. Rationale:

The Framingham Study is well known for the development of prediction equations that take into account the contribution of major risk factors (i.e. age, blood pressure, cigarette smoking, cholesterol, HDL-cholesterol and diabetes status) to an individual's risk of coronary heart disease (CHD). Additionally, a cardiovascular risk score has been developed that demonstrates the ability of traditional risk factors to predict 10-year risk of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study (*Chambless et al. Journal of Clinical Epidemiology. 2003; 56:880-90*). Unlike the

Framingham risk score, the ARIC risk score establishes the contribution of traditional risk factors to CHD risk in Blacks.

Increasingly, studies have evaluated whether nontraditional risk factors (i.e. C-reactive protein, lipoproteins, BMI, heart rate, etc.) improve prediction of individual risk of CHD beyond traditional risk factors (*Folsom et al. C-reactive protein and other novel risk factors add little to prediction of incident coronary heart disease in the ARIC cohort* and *Chambless et al. Journal of Clinical Epidemiology. 2003; 56:880-90*). This study will assess whether the contribution of genetic factors provides increased predictive ability of a CHD event beyond a cardiovascular risk score containing traditional risk factors.

The contribution of genetic factors to CHD risk will be assessed by the creation of a Genetic Risk Score (GRS). Genetic variation considered for inclusion in the GRS includes SNPs previously genotyped in the entire ARIC cohort as well as SNPs determined by Celera Diagnostics to play a role in cardiovascular risk, also genotyped in the entire ARIC cohort as a part of Ancillary Study 2004.11. The measure of the predictability of a risk score for an individual is the area under the ROC curve (AUC). Race-specific AUCs will be calculated and compared for prediction equations containing the tradition risk factors determined for the ARIC cardiovascular risk score as well as for the inclusion of the genetic risk score in the prediction equation.

5. Main Hypothesis/Study Questions:

Main hypothesis: An individual's genetic risk score improves predictive ability of a CHD event beyond traditional risk factors.

Study Questions:

1. Within Whites and Blacks, the significance of a race-specific genetic risk score will be evaluated by a Cox proportional hazards model for CHD that includes traditional CHD risk factors (i.e. age, systolic blood pressure, use of hypertension medication, total cholesterol, HDL-cholesterol, diabetes status, smoking status and gender).
2. A ROC curve and the corresponding AUC will be determined for a risk score prediction equation containing traditional risk factors, within each race. Similarly, a ROC curve and corresponding AUC will be determined for a prediction equation additionally containing the race-specific genetic risk score. The AUCs will be compared to determine whether inclusion of the genetic risk score improves prediction of a CHD event.
3. Within each race, individuals will be stratified with regard to their cardiovascular risk score (containing only traditional risk factors). The significance of the genetic risk score will be evaluated within each tertile by a Cox proportional hazards model adjusting for age and gender.

6. Data (variables, time window, source, inclusions/exclusions):

Incident CHD cases up to 1998 (i.e. 10-year follow-up) will be identified from the inc_by01 dataset.

Traditional risk factors utilized for the cardiovascular risk score include age, systolic blood pressure, hypertension medication use (HYPTMD01), total cholesterol, HDL-cholesterol, diabetes status (DIABTS03), smoking status (CURSMOK01) and gender. Genetic variation contributing to the genetic risk score includes SNPs previously genotyped in the entire ARIC cohort as well as SNPs determined by Celera Diagnostics to play a role in cardiovascular risk, also genotyped in the entire ARIC cohort as a part of Ancillary Study 2004.11.

Exclusions prior to analysis involve the removal of individuals with existing or missing data for prevalent CHD at baseline, diagnosis or history of stroke at baseline, Blacks not from Jackson, MS, race other than Black or White, and individuals with restricted DNA use. Additional exclusions will be performed for individuals missing data for any one of the nontraditional risk factors or BMI.

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

b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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? __X__ 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 ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
__X__ 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.cscc.unc.edu/ARIC/search.php

__X__ Yes _____ No

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? __X__ Yes ____ No

11.b. If yes, is the proposal

_X_ A. primarily the result of an ancillary study (list number* 2004.11)

___ B. primiarly 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.cscc.unc.edu/aric/forms/

12. 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.