ARIC Manuscript Proposal # 1291

PC Reviewed: 10/09/07  Status: A  Priority: 2
SC Reviewed:  Status:  Priority: 

1.a. Full Title: The clinical utility of genetic risk score in reclassifying risk for incident CHD in the ARIC study

b. Abbreviated Title (Length 26 characters): CHD genetic risk assessment and reclassifying risk

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _____ [please confirm with your initials electronically or in writing]

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3. **Timeline:** Analysis to start as soon as approval is obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the analysis and manuscript preparation will take place within 1 year from approval of the proposal.

4. **Rationale:** Prediction of coronary heart disease (CHD) is based on well-established and commonly measured risk factors which are also called “traditional” risk factors. A large number of studies have shown association of single nucleotide polymorphisms (SNPs) and the risk for CHD. Most of the SNPs that were found to be associated with CHD had only a slight impact on the overall risk, although a few, like the recently reported 58-kilobase interval on chromosome 9p21 (McPherson et al, Science, 2007), have been shown to have substantial association with CHD. In an attempt to sum the different SNPs and their impact on CHD, a genetic risk score (GRS), encompassing 10 genes for whites and 11 for blacks, based on the ARIC study has been recently published by Morrison et al. The GRS, in addition to the conventional risk factors, has been shown to have a significant impact on prediction of CHD in blacks and in some cases in whites.

We would like to investigate the direct influence of the GRS, with and without the addition of the recent discovery of SNPs in chromosome 9p21 region, on the CHD risk of the individual, to study how this will influences clinical classification and what would be the practical outcome of such reclassification. In addition, we would examine the cost-effectiveness of such a test.

We hypothesize that investigation of 9p21 region with and without the GRS (making up an enhanced GRS [EGRS]) will improve risk classification (i.e., refine classification of patients thought to be intermediate, low, or high risk based on “traditional” risk factors using Framingham/ARIC risk scores) and influence medical management strategy based on the Adult Treatment Panel III (ATP III) treatment guidelines. Reclassification would particularly influence treatment decisions in individuals who are considered to be at intermediate risk by traditional risk factors but who are reclassified as high risk or low risk by EGRS.

5. **Main Hypothesis/Study Questions:**

   **Hypothesis:** SNP testing in the 9p21 appropriate region and the EGRS when added to traditional risk scores such as the ARIC risk score (ARS) will improve classification of patients in the various risk groups.

   **Questions to be addressed in a stepwise manner:**
   1. Will the addition of SNPs for 9p21 (as observed by McPherson et al, Science, 2007) improve risk classification of individuals for CHD better than the use of traditional risk factors?
   2. Will SNP evaluation for 9p21 (as observed by McPherson et al, Science, 2007) added to the published GRS and calculated to an EGRS improve risk classification beyond GRS alone?
   3. How will using the GRS influence risk reclassification, and then, applying this new risk classification to the ATP III treatment guidelines, how many individuals would actually require a change in therapy based on the data available in ARIC?
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).

After excluding patients with CHD and stroke at baseline and those who have not provided consent for use of genetic information, all the other patients in the ARIC study on whom ARS can be calculated and who have available relevant SNP testing will be eligible for the analysis. In addition, EGRS will be evaluated specific for a particular gender and race.

We would:

1. Define the ARS at baseline and classify as low (10-year CHD risk ≤5%), intermediate (10-year CHD risk 5–20%), and high (10-year CHD risk >20%). Also classify patients as defined in ATP III, i.e., intermediate risk as 10-year CHD risk of 10–20%.

2. Describe the incident CHD events (cardiovascular death, myocardial infarction, and revascularization) in the different categories of ARS and then stratify them based on the EGRS. We will perform analyses separately for African Americans and Caucasians.

3. Using the Cox proportional hazards model, fit models with traditional ARIC risk factors with the following: (1) with the addition of 9p21 region SNPs alone; (2) with EGRS (GRS + 9p21 region). We will then examine the effect on reclassifying risk for incident cardiovascular events including cardiovascular death, myocardial infarction, and coronary artery or cerebrovascular revascularization. We will perform analyses separately for African Americans and Caucasians. In light of the low frequency of women who have intermediate risk scores, we will also perform analyses for the population as a whole and then separately for men and women in regard to reclassification. We will then compute the area under the curve for the models with and without 9p21/EGRS. Then, to assess model calibration or how closely the predicted probabilities reflect actual risk, the following strategies will be applied:
   i. Calculate the actual observed risk and then compute the Gronnesby-Borgan test comparing the observed and predicted risk using participant’s actual follow-up time, with 10 categories based on 2% point increases in predicted risk ranging from <2% to 18% with and without 9p21/EGRS. Also compute the statistic using decile categories of predicted probabilities. Clinical utility will be estimated by comparing predicted risk estimates based on models using ARS with and without 9p21/EGRS and then using weighted kappa statistics to compare the predicted probabilities with and without 9p21/EGRS. Group the predicted probabilities into 10-year risk categories of 0 to <5%, 5 to <10%, 10% to <20%, and ≥20%. Generate a table as below to describe the same:

<table>
<thead>
<tr>
<th>10 year risk without genetic evaluation</th>
<th>10 year risk with 9p21 or EGRS total reclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt;5%</td>
<td>0 to &lt;5%</td>
</tr>
<tr>
<td>5 to &lt;10%</td>
<td>5 to &lt;10%</td>
</tr>
<tr>
<td>10% to &lt;20%</td>
<td>10% to &lt;20%</td>
</tr>
<tr>
<td>≥20%</td>
<td>≥20%</td>
</tr>
</tbody>
</table>
In addition we will show percentages of participants reclassified and their recomputed predicted risk.

ii. Another strategy that will be used to compare observed and predicted risk is to use a Kaplan-Meier curve (not modeling with risk factors) to get a 10-year observed risk estimation for the cells of the table. We can also obtain predicted risk using traditional risk factors. Following this we will obtain a 10 year predicted risk using the new risk score (EGRS). We will then compare this to the 10-year observed risk based on the Kaplan-Meier estimate. The problem with this strategy is that it may evidence the variability of the small samples.

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 _x__ 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 _x__ 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.csecc.unc.edu/ARIC/search.php
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*)
   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.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.