**ARIC Manuscript Proposal #2047**

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| **PC Reviewed: 12/11/12** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Association of a cystatin C gene variant with cystatin C levels, chronic kidney disease, and risk of incident cardiovascular disease and mortality

**b. Abbreviated Title (Length 26 characters)**: cystatin C variant adjust

**2. Writing Group**:
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We would like to submit a proposal to test whether adjusting the cystatin C eGFR equation for a genetic variant associated with cystatin C but not kidney function will improve risk stratification.

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

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**3. Timeline**:
Starting Analyses: May 2012
First Draft: December 2012
Submission for Publication: January, 2013

## 4. Rationale:

Reduced glomerular filtration rate (GFR) is a risk factor for end-stage renal disease, cardiovascular disease and all-cause mortality.[1] Cystatin C is an alternative biomarker of kidney function with several physiological advantages over creatinine, including a stable, tightly-regulated rate of appearance in the circulation, less affected by muscle mass, and undetectable tubular secretion.[2] However, there are other non-kidney related factors that affect cystatin C metabolism.

The cystatin C gene cluster polymorphism, rs13038305, was the index SNP in a recent genome-wide association study of cystatin-based estimated glomerular filtration rate (eGFRcys) conducted in over 12,000 individuals of European ancestry.[3] Each copy of the T allele is associated with 6% increase in eGFRcys. However, this variant was not associated with creatinine-based eGFR (eGFRcrea). Therefore, it is likely that rs13038305 is related to cystatin C production, instead of kidney function.

We hypothesized that adjustment for this genetic effect on eGFRcys would improve GFR estimation and meaningfully reclassify individuals across categories of chronic kidney disease (CKD). We additionally sought to evaluate whether genotype-adjusted eGFRcys has stronger associations with important adverse outcomes of CKD, namely incident cardiovascular disease and death, which would be indicative of a refinement in GFR estimation by eliminating genetic noise.

## 5. Main Hypothesis/Study Questions:

Adjusting eGFRcys for rs13038305 would improve GFR estimation and meaningfully reclassify individuals across categories of CKD. We further hypothesize reclassification to higher CKD risk category based on genotype-adjusted eGFRcys will associated with higher risk of mortality and cardiovascular events.

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

Cohorts**:** CHS, ARIC, FHS, HABC

Individuals with self-reported white race, cystatin C levels and completed genotyping

**Analysis Plan**

1. Calculate creatinine-based eGFR and cystatin-C based eGFR using the recently published CKD-EPI equations. [4]
2. Perform association analyses of rs13038305 with measures of kidney function (eGFRcys and eGFRcrea).

3. Perform meta-analysis across the 4 participating cohorts to obtain the beta estimate of the association of rs13038305 with eGFRcys based on the CKD-EPI cystatin C equation.
4. Calculate a genotype-adjusted eGFRcys based on rs13038305 beta estimate from the meta-analysis result in step 3.
5. Perform the following analyses in each participating cohort using unadjusted and genotype-adjusted eGFRcys, then combine the results in inverse variance fixed effect meta-analysis:
   A. Net reclassication improvement (NRI) analysis[5] using eGFRcys categories at cut points of 45, 60 and 90 using mortality or cardiovascular events as outcomes
   B. Survival analysis using proportional hazard model to compare the risk of mortality or incident cardiovascular events among those reclassified based on genotype-adjusted eGFRcys versus those with no reclassification. Incident cardiovascular events include stroke, MI, CV death, excluding silent MI, TIA and hemorrhagic CVA.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**
**__X__ Yes ___ _ 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?**
**__X__ 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)?**

Will contact the members of the work groups on CKD???

**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 (2004.10 )**

**___ 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.**

References


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2. **Shlipak MG, Katz R, Sarnak MJ, Fried LF, Newman AB, Stehman-Breen C, Seliger SL, Kestenbaum B, Psaty B, Tracy RP, Siscovick DS. Cystatin c and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med*. 2006;145:237-246**
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4. **Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS. Estimating glomerular filtration rate from serum creatinine and cystatin c. *N Engl J Med*. 2012;367:20-29**
5. **Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: From area under the roc curve to reclassification and beyond. *Stat Med*. 2008;27:157-172; discussion 207-112**