ARIC Manuscript Proposal # 1692

PC Reviewed: 9/14/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Identification of urinary biomarkers for incident chronic kidney disease

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

Writing group members: Anna Kottgen, Brad Astor, Hunter Young, Joe Coresh, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. AK **[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: measurement of metabolites in urine in fall/winter of 2010, data cleaning and analysis to start upon receipt of the data.

4. Rationale: The kidney is a key excretory organ of the human body. It generates approximately 180 liters of ultrafiltrate each day to clear external substances and metabolic products from the blood. As kidney function deteriorates, the excretory as well as other functions of the kidney can be impaired.

The most commonly used marker of kidney function, serum creatinine, typically increases in serum only after about 50% of the kidney's filtration function has been lost.

In light of the high prevalence of reduced kidney function and chronic kidney disease (CKD),(1) it is of interest to identify biomarkers that are associated with earlier renal function decline, incident CKD and end-stage renal disease (ESRD).

Urine contains numerous metabolites excreted by the kidney, and therefore provides an excellent resource to perform an unbiased search for kidney-disease associated markers. Early studies using metabolomics to identify small disease-associated molecules in urine have been conducted among diverse groups of patients, including patients with cancers of the kidney(2) and patients with rare genetic diseases of the kidney.(3) Recently, a study conducted metabolite profiling in serum to identify biomarkers of ESRD and highlighted the role of uremic dyslipidemia and the biochemical effects of hemodialysis in this patient population.(4) To the best of our knowledge, no studies have been conducted that study urine from incident ESRD cases and controls from a general population-based sample in order to identify small metabolites that are associated with incident CKD and ESRD.

5. Main Hypothesis/Study Questions:

1. Are there differences in the baseline urinary metabolite profile between cases with incident ESRD and age- and sex-matched controls?
2. Are any such markers associated with continuous measures of kidney function, estimated glomerular filtration rate and the urinary albumin-to-creatinine ratio, among the controls?
3. Do any such markers belong to a certain metabolic pathway, thus highlighting the role of this pathway in ESRD?

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).

Urine samples were collected at ARIC visit 4 (1996-98), which will represent the baseline for our analyses. Therefore, individuals who did not attend visit 4 or are missing urine samples will be excluded. Further, individuals missing serum creatinine or of self-reported race other than white or black will be excluded.

Cases will be defined as those with incident ESRD after Visit 4 identified from ICD codes on hospitalization discharge records (ICD-9) and death certificates (ICD-9 and -10) through January 1, 2007. Controls will be matched to cases using frequency matching for age, sex, race, diabetes and eGFR (10 ml/min/1.73m^2 windows). If sufficient funds are available, the case-control design will be expanded to include cases of incident CKD (defined as GFR <60 ml/min/1.73m^2 at the ARIC carMRI visit among those with eGFR >60 ml/min/1.73m^2) at Visit 4).

Urine metabolites will be measured from stored frozen urine samples at Imperial College (London, UK) by the group of Elaine Holmes. Urine samples are shipped for measurement as part of a funded ARIC ancillary study aiming to identify urine metabolites associated with incident diabetes (PI H. Young, #2009.02)

Covariates of interest will include fasting glucose, blood pressure measurements, BMI, plasma lipids, smoking, and intake of medications.

All analyses will account for the matching and selection of controls. Statistical analyses will include comparison of metabolite concentrations and/or their ratios in cases and controls. To account for differences in urine concentration, metabolite concentrations will be indexed to urinary creatinine. Conditional logistic regression will be used to identify metabolic predictors of ESRD status.

Since there is little experience with data analysis from urine metabolomics projects, challenges relate to the identification of an appropriate way to account for differences in urine concentration between individuals as well as to account for the correlation of metabolites from the same biochemical pathway.

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 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 ICTDER03 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 _X_ 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.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)?

#1544: Urinary proteins and incident chronic kidney disease (Astor)

1574: Comparison of novel markers of kidney function and prediction of cardiovascular events, mortality, and kidney failure: the Atherosclerosis Risk in

Communities (ARIC) Study (Astor)

#1581: Novel markers of kidney function and prediction of incident chronic kidney disease and end-stage renal disease: the Atherosclerosis Risk in Communities (ARIC) Study (Astor)

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

___ A. primarily the result of an ancillary study (list number* __2006.16, #2009.02**)**

___ 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

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA : the journal of the American Medical Association. 2007 Nov 7;298(17):2038-47.
2. Kind T, Tolstikov V, Fiehn O, Weiss RH. A comprehensive urinary metabolomic approach for identifying kidney cancerr. Anal Biochem. 2007 Apr 15;363(2):185-95.
3. Tzovaras VT, Psychogios NG, Kostara CE, Bairaktari ET, Elisaf MS. Evaluation of the proximal tubular function in individuals with primary renal hypouricemia: an NMR-based metabonomic study. NMR Biomed. 2009 Dec;22(10):1072-83.
4. Rhee EP, Souza A, Farrell L, et al. Metabolite profiling identifies markers of uremia. J Am Soc Nephrol. Jun;21(6):1041-51.