ARIC Manuscript Proposal # 1753

PC Reviewed: 2/8/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Genome-Wide Association Study of Longitudinal Change in Pulmonary Function: Meta-Analysis in the CHARGE and SpiroMeta Consortia**

b. Abbreviated Title (Length 26 characters): **GWAS of Change in PFTs**

2. Writing Group:

Writing group members: Bonnie Joubert, Nora Transceschini, Laura Loehr, Kari North, Alanna Morrison, David Couper, Aaron Folsom, Stephanie London and other interested ARIC investigators with time to contribute*.

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

First ARIC author*: **Bonnie Joubert, Postdoctoral Fellow NIEHS**
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*Note – this manuscript is being lead by Dr. Pat Cassano and her collaborators from Health-ABC within the CHARGE consortium. They drafted an initial analysis plan which was then refined in several iterations of input from the CHARGE pulmonary group (see attached). The ARIC lead authors will not be the lead authors for the paper. In addition to the CHARGE cohorts, the paper will include cohorts from the European SpiroMeta consortium and hopefully additional European cohorts who have been participating in some recent meta-analysis with CHARGE and SpiroMeta. It is not yet clear which cohorts will be included in starred first and starred last authorships and it is not yet clear how many individual authors will be listed per cohort.

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: Begin ARIC analysis March 2011. The ARIC investigators will be responsible for running the GWAS with the ARIC data according to the analysis plan agreed upon by the CHARGE pulmonary group. Drs. Joubert and London will be responsible for the computation required for the ARIC analysis and all ARIC authors will assist with checking results and providing input. The GWAS betas and P values will be uploaded to the the CHARGE sharepoint. Pat Cassano of Health ABC (CHARGE) and her team will perform the meta-analysis once all of the participating cohorts have uploaded their GWAS results. We would hope that a manuscript would be ready to submit to the ARIC manuscript committee by February 2012 but the timeline will not be completely under our control because Dr. Cassano is leading this meta-analysis requiring the cooperation of many different analysts.

4. Rationale: Recent genome-wide association studies of cross-sectional measures of pulmonary function have identified a number of novel loci. The first gene identified was the HHIP gene (1). A later meta-analysis from the CHARGE Consortium (ARIC MS #1357) identified an additional 8 novel loci and confirmed HHIP (2). Pulmonary function at a given point in adult reflects factors that influence lung and airway growth to early adulthood and then factors that influence the inevitable age-related decline. The genes identified in GWAS of cross-sectional pulmonary function are weighted toward those involved in growth and development. There are no published data from genome wide association studies on longitudinal decline in pulmonary function. However, ARIC participated in look-up replication of top hits for the ESE consortium (MS # 1676). Although this paper is not yet complete, the results suggest that distinct genes underlie cross-sectional pulmonary function and its decline with age. We speculate that genes involved in pulmonary response to environmental agents might be related to decline in pulmonary function more strongly than genes involved in development. To date candidate gene studies have not been fruitful. As was the case with cross-sectional pulmonary function, we expect that GWAS may identify novel genetic associations with longitudinal measures.

5. Main Hypothesis/Study Questions:

We are asking whether genome wide association analysis will identify novel genetic variants related to the rate of decline in pulmonary function.

The primary parameter of interest is the FEV1 (forced expiratory volume in one second). This is the pulmonary function parameter that is typically followed with respect to decline. However, it is possible that reviewers or editors may request analyses of the other major pulmonary function parameters – FVC and the FEV1/FVC. Therefore it is possible that we might need to include analysis of these parameters in the manuscript.

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).

A detailed analysis plan (**ATTACHED**) has been developed by Drs Pat Cassano, Wenbo Tang and Marty Wells (all of Cornell University). These investigators represent the HEALTH-ABC cohort (longitudinal study of aging) in CHARGE and had previously performed a longitudinal analysis in HEALTH-ABC. They are taking the lead on this meta-analysis for the CHARGE group. The analysis plan was refined based on interactive feedback from the CHARGE Pulmonary Group on several phone conferences and by email afterwards. Dr. Cassano will seek additional cohorts outside of CHARGE to participate either in the meta-analysis or for look-up replication, depending on their level of interest. She will first look for collaborators within the SpiroMeta consortium who have recently been collaborating with the CHARGE pulmonary group. However, given that there are few SpiroMeta cohorts with longitudinal data she will also look to additional cohorts with longitudinal pulmonary function data such as the ESE consortium for whom we participate for look-up replication (MS# 1676).

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 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? __x__ 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? _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 ICTDER03 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)?

The lead author (Stephanie London) heads the CHARGE Pulmonary Group which has several manuscript proposals completed or ongoing. Please see below.

1676 Look-up replication in ARIC of top findings from genome wide association study (GWAS) of decline in pulmonary function in the ESE consortium. S. London

The above manuscript proposal was to do look-up replication for another group that was leading a GWAS.

1597 Genome-wide association study of pulmonary function: joint meta-analysis of two consortia - CHARGE and SpiroMeta. S. London

The above manuscript proposal was limited to cross-sectional analysis.

#1562. Genome Wide Association Study of interaction with smoking in relation to pulmonary function and COPD. D. Hancock working with S. London. This manuscript will be restricted to cross-sectional analysis.

#1357 Genome-Wide Association Study (GWAS) of Pulmonary Function and Chronic Obstructive Pulmonary Disease (COPD) – interaction with intake of fiber and other nutrients in ARIC. S. London. This manuscript proposal was merged with #1360 and resulted in the publication of Hancock et al. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. Nat Genet. 2010 Jan;42(1):45-52. Epub 2009 Dec 13.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ 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.

References:

1. Wilk JB, Chen TH, Gottlieb DJ, Walter RE, Nagle MW, Brandler BJ, Myers RH, Borecki IB, Silverman EK, Weiss ST, O'Connor GT. A genome-wide association study of pulmonary function measures in the Framingham Heart Study. PLoS Genet. 2009;5(3):e1000429. PMCID: 2652834.

2. Hancock DB, Eijgelsheim M, Wilk JB, Gharib SA, Loehr LR, Marciante KD, Franceschini N, van Durme YM, Chen TH, Barr RG, Schabath MB, Couper DJ, Brusselle GG, Psaty BM, van Duijn CM, Rotter JI, Uitterlinden AG, Hofman A, Punjabi NM, Rivadeneira F, Morrison AC, Enright PL, North KE, Heckbert SR, Lumley T, Stricker BH, O'Connor GT, London SJ. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. Nat Genet. 2010;42(1):45-52. PMCID: 2832852.