ARIC Manuscript Proposal # 1676

PC Reviewed: 8/10/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Look-up replication in ARIC of top findings from genome wide association study (GWAS) of decline in pulmonary function in the ESE consortium.

b. Abbreviated Title (Length 26 characters): **Replication–PFT decline GWAS**

2. Writing Group:

Writing group members: Stephanie London, Dana Hancock, Laura Loehr, Nora Fransceschini, Kari North

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _SJL____ **[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: Start as soon as approval is obtained. Replication cohorts need to complete work within four weeks of signing agreement. In order to participate, we need to provide the results to the consortium investigators (ESE – see below) by September 4, 2010.

4. Rationale:

ARIC investigators recently led a genome wide association study (GWAS) of baseline (cross-sectional) pulmonary function within the CHARGE consortium (Hancock et al., Nature Genetics 2010;42:45). Pulmonary function in adults reflects a combination of growth to maximal attained pulmonary function (between ages 18-25) and decline with age thereafter. The findings in our GWAS of cross-sectional pulmonary function appear to be dominated by genes involved in growth. Earlier linkage studies suggested that different genes are involved in determination of cross-sectional pulmonary function versus rate of decline with age in adulthood. It is therefore of interest to do GWA analysis of the rate of decline in pulmonary function.

A European consortium (ESE) of three studies has completed a GWAS of rate of decline of pulmonary function. The subjects in the ESE are adults aged 18 years to 70 years of Caucasian origin. The three component studies are the French EGEA study which has a family-based design, and SAPALDIA and ECRHS , which are population-based. Data for these three studies was derived from two surveys performed at baseline and follow-up roughly 10 years apart. The ESE investigators are now requesting other cohorts of Caucasians with GWA data to serve in the look-up replication phase.

The ESE lead investigator Nicole Probst-Hensch **would send us 35 SNPs to analyze from our GWAS genotyping data. They are specifying the analysis. They will allow up to five authors from the ARIC cohort on the resulting publication. We have not yet signed the ESE data agreement (since we do not have ARIC approval) so we do not know the nature of their top hits and what level of significance they have. Of note, SAPALDIA has agreed to participate in lookup replication that our CHARGE group has requested for ongoing analyses of COPD and GWAS*smoking. ECHRS is participating in meta-analysis with us in these two papers. Their data are of very high quality.**

ARIC has two measures of pulmonary function done three years apart (visits 1 and 2). Although in the occupational screening literature it has long been stated that one cannot properly examine decline in pulmonary function with an interval of less than four years (Vollmer WM, Occup Med 1993;83:339) due to measurement error, this dictum relates to clinical interpretation of the results in individuals. The ARIC data are suitable for epidemiologic analyses - rates of decline in FEV1 and FEV1/FVC in ARIC have expected relationships with age and smoking. The ESE is very interested in including the ARIC data and they are aware of the three-year interval between visits.

5. Main Hypothesis/Study Questions:

Do top SNPs identified in GWAS of rate of decline of pulmonary function in the ESE consortium confirm in the ARIC study and in other adult populations? The three pulmonary function parameters that they are asking us to examine are FEV, FVC and FEV1/FVC.

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).

ESE is requesting analysis of 35 SNPs in relation to lung function decline modeled using sex-and asthma-specific standardized residuals, adjusted for age, height and study center.

Main covariates: Age, height and study center are used for the calculation of sex- and asthma-specific residuals of decline in FEV1, FVC and FEV1/FVC ratio. Principal components are used at the genetic analysis level to account for population stratification.

We will exclude individuals with age > 70 at visit 2 per the specifications of ESE.

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)?

Most related are several proposal on which Dr. London in the contact investigator. These proposals use cross-sectional, not longitudinal pulmonary function data:
1597 Genome-wide association study of pulmonary function: joint meta- analysis of two consortia – CHARGE and SpiroMeta.
1562 Genome Wide Association Study of interaction with smoking in relation to pulmonary function and COPD.
1357 Genome-Wide Association Study (GWAS) of Pulmonary Function and Chronic Obstructive Pulmonary Disease (COPD). – resulted in Hancock et al. **Nature Genetics 2010;42:45.** A separate manuscript for COPD (with the CHARGE consortium) is approved under this same MS proposal number.

We will soon be submitting a proposal for a primary analysis of longitudinal decline in pulmonary function in the CHARGE and SpiroMeta consortia.

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.