ARIC Manuscript Proposal #3504

PC Reviewed: 11/12/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Derivation of a machine learning based score predictive of MCI and Dementia in the Atherosclerosis Risk in Communities (ARIC) cohort

b. Abbreviated Title (Length 26 characters): Machine learning & dementia

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

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3. Timeline:

Expectations are for analyses to be completed within 1 year.

4. Rationale:

Structural MRI (sMRI) is an imaging modality used to study characteristic patterns of brain tissue atrophy resulting from cumulative loss and shrinkage of the neuropil. As an indicator of neuronal injury resulting from different causes, it is not necessarily AD-specific[1]. sMRI has been used to investigate AD patterns of tissue atrophy by employing voxel-based morphometry (VBM), tensor-based morphometry[2, 3] and region of interest (ROI) analyses, often based on hippocampal volume[4]. VBM was developed as an alternative to ROI analyses because it can capture complex patterns across ROIs that will be missed by standard ROI methods. Voxel-based methods use segmentations of gray matter (GM) and/or white matter tissue and/or cerebrospinal fluid (CSF) at the voxel level.[5, 6] These types of approaches are in essence univariate and based on traditional statistics; they do not allow for individual-level predictions, which would be desirable from a clinical perspective.

Machine learning methods can address the challenges posed by the high dimensionality of neuroimaging data and other sources of information that must be integrated to produce accurate prediction models. Machine learning is a branch of **artificial intelligence** that deals with development of algorithms to make intelligent data-based decisions or uncover complex patterns hidden in data. They are multivariate and often non-linear, which expands the potential to capture complex functional relationships within datasets. **Machine learning methods that operate directly at the voxel level should have an advantage over ROI- based approaches**, since they can capture complex spatial patterns of atrophy that extend across ROIs. Although several research groups[7-9] (including ours) have used machine learning to derive whole brain biomarkers of AD-related neurodegeneration only a very few have been validated and are well documented. For example, the SPARE-AD index has been tested for associations with plasma analytes[10], prediction of incident impairment[11] and replicated in a second database[12, 13].

We have developed the AD Pattern Similarity (AD-PS) Scores, first applied to the Alzheimer's Disease Neuroimaging Initiative cohort and more recently to the Women Health Initiative Memory (WHIMS) MRI study[14, 15]. Our approach is based on an elastic net regularized classifier. The sparsity property of the elastic net algorithm means that the coefficients of voxels in the model irrelevant to prediction are forced to be zero, which is equivalent to an embedded variable selection mechanism. Because of the sparsity constraints, the algorithm can determine by itself, based on the imaging data, the brain areas relevant for prediction of AD. The AD-PS scores have shown strong associations with incident cognitive impairment and cross-sectional and longitudinal associations with age, cognitive function, cognitive status and white matter small vessel ischemic disease volume[15]. In addition, a recent report from our group [16] found the AD-PS scores to be associated with trajectories of cognitive function in WHIMS-MRI. Women were grouped into five clusters of trajectories using a latent class approach[17]. AD-PS scores varied significantly among clusters of trajectories with relationships that were more consistent and stronger than those for other traditional risk factors (education, diabetes, and *APOE*-ε4 genotype).

Other approaches have focused on combinations of regions of the brain known to be vulnerable to AD apriori. For example, other ARIC researchers used an AD-signature MRI

biomarker based on volumes of several brain areas (e.g. Hippocampus, entorhinal, parahippocampal, precuneus, cuneus and inferior parietal lobule) known to be related to AD[18, 19].

The relative predictive value of different measures developed using machine learning or based on human expertise is unclear. We will estimate the AD-PS scores for visits 5 MRI scans and take advantage of the availability of the AD-signature in ARIC to compare their relative merit when predicting cognitive status an incident cognitive impairment. In addition, we will take advantage of the availability of amyloid PET in ARIC to investigate associations of the MRI measures with amyloid burden in a subset of ARIC participants[20].

5. Main Hypothesis/Study Questions:

Our main goal is estimating the AD-PS scores for the ARIC MRI cohort and investigate associations with cognitive status, incident cognitive impairment and amyloid burden. In addition, we will compare their relative merit with respect to the AD-signature biomarker when predicting cognitive status and incidence of MCI and AD in the ARIC MRI cohort. Our main hypotheses are:

Hypothesis 1: The AD-PS scores estimated at visit 5 will be associated with cognitive status at visit 5 for all participants with MRI. (Cross-sectional, n=1971)

Hypothesis 2: The AD-PS scores estimated at visit 5 will be associated with PET amyloid global cortical standardized uptake value ratios. (Cross-sectional, n=329)

Hypothesis 3: The AD-PS scores estimated at visit 5 will be predictive of incident cognitive impairment at visits 6 and 7 for those participants with MRI and adjudicated as cognitively normal at visit 5. (Longitudinal)

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).

Design: Cross-sectional design for neuroimaging and baseline cognition and a longitudinal study design for cognitive changes over follow-up through visit 7.

Outcome sets:

Visits 5-7
Demographic data
Cognitive data
Adjudication of cognitive status
APOE Ɛ4 carrier status

Datasets:

Visits 5:

T1 MRI raw images for all individuals
Lesion burden information: White matter hyperintensities, infarcts, microhemorrages, etc.
Amyloid PET - ROI SURVs
AD-signature volumes
Hippocampal volumes
Intracranial volumes

Estimation of the AD-PS scores

T1 MRI images available in ADNI and ARIC will be processed using a pipeline based on Advanced Normalization Tools (ANTs)[21, 22] that we have developed[15]. We can use a cluster of over 1500 CPUs using the Slurm scheduler. ANTs' capabilities include diffeomorphic transformations for image warping that preserve topology. These are based on symmetric normalization algorithms which have been top-performing image warping approaches in large comparative studies[23, 24]. As a result of the processing, segmented images representing different tissues will be warped into a common template. In this case, the common template for both studies will be generated using images from ADNI-2 CN participants. The rest of the ADNI and ARIC MRI images will be warped directly to the ADNI template. Technical details about ANTs processing and our Slurm pipeline can be found elsewhere[21, 25]

Once ADNI and ARIC MRI images are aligned into a template, we will use high-dimensional machine learning methods to estimate AD-PS scores in the ARIC cohort as described in [15]. Further details of the machine learning algorithms were published previously[26, 27]. Briefly, an elastic net regularized logistic regression (EN-RLR) classifier was estimated using the GM probability maps from CN and AD participants in ADNI; in other words, ADNI is used as training dataset. AD-PS scores are the class-conditional probability of membership to the AD group. These are computed as the median values of 5 repetitions of the computations, to account for variability due to random partitioning of cross-validation that occurred during model estimation[26]. The AD-PS scores for ARIC participants are estimated by providing their corresponding visit 5 GM probability maps to the ADNI-based classifiers.

Analyses:

1) Logistic regressions, linear regressions, and Cox proportional hazards regressions will be used to investigate the scores associations with cross-sectional cognitive status and amyloid burden, and incidence of cognitive impairment, respectively. These analyses will be adjusted by age, race, sex, education and intracranial volume.
2) The impact of MRI measures of lesion burden (e.g. white matter hyperintensities, microhemorrages, infarcts, etc.) on these associations (MRI scores with cognitive status, incident cognitive impairment and amyloid burden) will be evaluated.

Comparisons:

The AD-PS and AD-signature scores will be standardized. They will be treated as independent variables and fitted in linear, logistic and Cox proportional hazards regression models one at a time. Age, sex, race, education, and intracranial volume will be adjusted in the models. Standardized regression coefficients and p-values will be calculated and compared. For logistic regressions, the area under curve (AUC) statistics will be estimated. The statistical differences in AUC statistics across models will be tested using the nonparametric method as well.[28] [28]

Exploratory analyses will be performed using stratifications by race, sex and APOE Ɛ4 carrier status

Limitations/Challenges

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 ICTDER 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)?

- #3118 - Comparison of existing methods for algorithmic classification of dementia status (Power)

- We are aware of a proposal under review by the P & P by Dr. Talluri and colleagues. Dr. Casanova is a co-author in that proposal.

These proposals though related seem to be complementary to ours that aims at investigating specific MRI biomarkers. However, we have invited Dr. Rajesh Talluri to be part of the writing group.

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

_x_ A. primarily the result of an ancillary study (list number* _2008-06_____)

___ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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