ARIC Manuscript Proposal #4169

PC Reviewed: 12/13/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Subtyping non-demented older adults based on changes in white matter microstructure over time by DTI to identify high-risk subtypes for rapid cognitive decline

b. Abbreviated Title (Length 26 characters):
Longitudinal DTI subtyping

2. Writing Group [please provide a middle name if available; EX: Adam Lee Williams]:
Yuto Uchida, Kenichi Oishi, Bruce Wasserman, Wenjie Yang, Kengo Onda, Jill Chotiyanonta, Ye Qiao

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

First author [please provide a middle name if available; EX: Adam Lee Williams]:
Address: 720 Rutland Ave., 330 Traylor Building, Baltimore, MD 21205, USA

Yuto Uchida
Phone: (410)502-3553 Fax:(410)614-1948
E-mail: yuchida2@jhmi.edu

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).
Name: Bruce Wasserman
Address: HSF – III, Rm 8106, 670 W. Baltimore Street, Baltimore, MD 21201

Phone: 410.706.2364 Fax:
E-mail: bwasser@som.umaryland.edu

3. Timeline:

Aims	specific activities	Year 1			Year 2		
	(months)	1 - 4	5 - 8	9 - 12	13 - 16	17 - 20	21 - 24
Aim 1	MRI/DTI processing	X	X	X			
brain	subgrouping (cognitive normal vs. rapid cognitive decline)	X	X				
phenotyping	group comparison			X	X		
Aim 2	clinical feature extraction from ARIC		X	X	X	X	
predictive	generation of prediction model				X	X	
modeling	model testing					X	X
	manuscript preparation						X

The project consists of two major components: (1) neuroanatomical and clinical feature extraction from the ARIC database; (2) generation of a prediction model and validation. The neuroanatomical features will be extracted by the multi-atlas library with cutting-edge multi-atlas label fusion (MALF) and linked to the clinical features extracted from ARIC. Only data that are already accessible to the ARIC Vascular Reading Center (PI, Dr. Wasserman) will be needed. No additional resources will be needed from the Coordinating Center. The manuscript will be complete within 24 months.

4. Rationale:

The medical costs of the elderly with dementia are approximately three times higher than those of the elderly without dementia. Identifying those at high risk of developing dementia in the non-demented elderly is critical because interventions such as cognitive stimulation therapy, tailored activity programs, and occupational therapy for the pre-dementia population have been demonstrated to reduce social costs by decreasing the annual conversion rate to dementia.

In older cohorts, significant variation in the degree of cognitive decline has been observed. Although the main cause of this variability is the pathological background of each individual, e.g., Alzheimer's disease (AD), vascular dementia (VD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD), it is important to note that even with the same pathological background, there are large individual differences in the rate of cognitive decline. Therefore, it is extremely important to identify groups of non-demented older adults who are at high risk of cognitive decline in the coming years so that early intervention can be provided.

Various types of biomarkers have been identified to predict cognitive worsening. Among them, structural MRI, especially 3D high-resolution T1-weighted images, is widely used as a source of research thanks to open resources for neuroimaging studies such as ADNI. However, it has been difficult to identify early changes associated with dementia, since atrophic changes seen on structural MRI reflect the consequences of neurodegeneration resulting from disease-specific pathological processes. On the other hand, white matter pathology seen in various types of dementia can be observed even in the very early stages of the disease without dementia, and even before the atrophic changes occur.

The distribution of white matter lesions is disease-specific, including changes in limbic fibers in AD, watershed distribution in VD, selective lesions in visual association areas and subcortical structures in DLB, and frontal and temporal lesions in FTD. Furthermore, even within the same disease category, there are subtypes with different patterns of white matter lesion distribution, reflecting clinical characteristics such as the rate of progression of cognitive decline. However, most existing disease classification studies are based on cross-sectional analyses, and the patterns identified may reflect patient groups observed at different disease stages. There is a lack of longitudinal studies of dementia subtypes to separate disease stages from disease subtypes.

5. Main Hypothesis/Study Questions:

Our long-term goal is to identify subgroups of older adults at high risk for rapid cognitive decline in the near future and to provide early intervention for these subgroups to slow the progression of

cognitive decline. Toward this goal, we proposed the following aims and hypotheses. **Aim 1:** To identify subtypes of longitudinal changes in white matter connectivity associated with rapid cognitive decline. The subjects' clinical and MRI data extracted from the ARIC longitudinal database will be used. A longitudinal DTI analysis will be applied to determine whether patients can be classified into subgroups at high risk for rapid cognitive decline according to the changes in white matter connectivity. **Hypothesis 1:** Changes in limbic, frontal, and temporal fibers are predictive of subgroups of older adults at high risk for rapid cognitive decline. **Aim 2:** To generate a predictive model for investigating modifiable risk factors associated with subgroups of older adults at high risk for rapid cognitive decline. A supervised learning analysis will be applied to the brain phenotypes to determine whether patients can be classified into subgroups at high risk for rapid cognitive decline. This supervised classification will also allow us to investigate associations between the clinical and neuroanatomical features. **Hypothesis 2:** There are subgroups of patients with similar brain phenotypes, severity of symptoms, age, and genotype, which can predict subgroups of older adults at high risk for rapid cognitive decline.

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).

This study will use diffusion tensor imaging (DTI) acquired at Visits 5, 6 and 7 to observe changes in white matter microstructure that occurred between Visit 5 and Visits 6/7, with the goal of assessing whether subtypes of white matter change during the observation period (mean 5.5 years) reflect specific cognitive trajectories. This is an important step toward discovering differences in pathological trajectories in older people. In addition, we will examine whether the identified subtypes are linked to specific modifiable environmental factors, thereby providing preliminary data for future intervention studies.

As a proof of concept, we will first extract preexisting resources, such as participants' demographics, cognitive scores and associated records, and MRI data, from ARIC longitudinal database to identify brain phenotypes and clinical features that might predict subgroups of older adults at high risk for rapid cognitive decline. These real-world data increase the likelihood that the findings will have a clinical application in broader settings. Second, our automated brain features extraction pipeline, which is robust to the huge heterogeneity in brain MRIs of diseased brains, will be used to quantify the diffusion characteristics of anatomical structures. We propose to develop a better understanding of clinical and neuro-anatomical features that may be associated with rapid cognitive decline.

Study subjects fulfill the following inclusion criteria: age ≥50 years, clinical dementia rating ≤0.5, and availability of results from neurocognitive testing acquired in ARIC and comprehensive MRI examinations, including structural and diffusion MRI sequences. Subjects with severe psychiatric illness or abnormal findings on brain imaging were excluded.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __✓__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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? ____ Yes _✓__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

___ 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)?

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 (list number* __2015.32___)
___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.