

## ARIC Manuscript Proposal #2948

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Priority: \_\_\_\_\_

**1.a. Full Title:** Patterns of morbidity and healthcare utilization preceding dementia and MCI diagnosis.

**b. Abbreviated Title (Length 26 characters):** Morbidity and care in dementia and MCI

### 2. Writing Group:

Writing group members: Anna Kucharska-Newton, Gerardo Heiss, David Knopman, A. Priya Palta, Michele Jonsson-Funk (invited), Brittany Bogle, Stephanie Haas. Others welcome.

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

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### 3. Timeline:

Manuscript draft planned for one year from proposal approval.

### 4. Rationale:

Dementia represents a compromise in a person's cognitive abilities and is diagnosed from evidence of substantial impairment to a person's memory and other cognitive domains. Estimates based on data for Medicare fee-for-service beneficiaries suggest that approximately 14% of adults 65 years of age or older have a diagnosis of dementia<sup>1,2</sup>. However, extant studies point to a significant underascertainment of dementia status in clinical practice<sup>3</sup>. Approximately 50% of dementia cases remain undiagnosed<sup>4</sup>, with higher rates of underdiagnosis observed among patients with low socioeconomic status and poor access to care.

Mild cognitive impairment (MCI) is a diagnostic category that defines an individual's cognitive status as outside of the normal age-appropriate cognitive functioning, but with intact functional abilities. Individuals with MCI are at high risk for developing dementia. Currently there is no effective treatment for MCI<sup>5</sup>; however, a diagnosis of MCI earlier in the course of progressive cognitive decline may provide an opportunity for risk factor modification and patient and caregiver engagement to delay progression of the disease. Most patients receive a diagnosis of dementia late in the course of the disease when the effectiveness of potential interventions is significantly diminished. Extant studies suggest that, in the absence of definitive therapeutic treatments, multidomain lifestyle interventions (i.e. diet and physical activity) and control of vascular (e.g. hypertension) and metabolic (e.g. diabetes) risk factors currently hold the greatest promise with respect to delaying the onset and progression of cognitive impairment<sup>6,7</sup>. An understanding of both the comorbidity burden preceding a diagnosis of cognitive impairment as well as patterns of care related to those comorbidities are important for characterizing patient and provider factors that may improve the effectiveness of such interventions.

While several studies suggest that comorbidity burden among patients with dementia is greater than that of age- and sex- matched cohorts of cognitively normal adults<sup>8,9</sup>, other studies provide evidence of comparable levels of comorbidities among those with, as compared to those without, a dementia diagnosis<sup>10</sup>. This lack of agreement is confounded by the cross-sectional nature of these prior studies examining comorbidity profiles in dementia, a design that is subject to reverse causality. Few studies examining comorbidity burden in the setting of dementia have considered disease severity in their assessments or objective ascertainment of comorbidities, and none have focused on mild cognitive impairment and pre-dementia states. Most of the interest in the clinical management of dementia has focused on use of healthcare services and expenditures incurred after a diagnosis of dementia has been made<sup>9,11,12</sup>. Relatively little is known about care preceding a dementia diagnosis<sup>13,14</sup> and even less about care preceding MCI<sup>15,16</sup>.

We propose to use the dementia classification at ARIC Visit 5, developed as part of the ARIC Neurocognitive Study (NCS), in combination with the linked ARIC CMS Medicare data, to examine comorbidities and patterns of healthcare use that precede the development of cognitive impairment (MCI and dementia). To answer our study questions, we propose to use machine learning methods, which will allow us to address the complexity of the comorbidity and healthcare use and their change over time to uncover patterns that may not have been apparent with traditional statistical approaches. All analyses will be conducted among participants enrolled in fee-for-service (FFS) Medicare at the time of Visit 5 and during at least 6 months prior to the visit.

## **5. Main Hypothesis/Study Questions:**

1. Using CMS Medicare claims and ARIC hospitalization records, describe evidence of clinical manifestation of cognitive impairment prior to the ARIC dementia and MCI classification.
2. Apply unsupervised machine learning protocols to identify patterns of comorbidities associated with care preceding ARIC dementia and MCI classification

## **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).**

### Study population:

All ARIC cohort participants with non-missing Level 1 dementia classification, enrolled in continuous Medicare Parts A and B (FFS Medicare) at the time of Visit 5 and for at least 6 months preceding the date of Visit 5 examination.

### Analytical considerations

#### **Aim 1**

#### ***Identification of dementia and MCI from CMS Medicare claims of ARIC cohort participants:***

Diagnostic codes: We will identify the presence of cognitive impairment in ARIC cohort participants' claims for clinical encounters occurring from the time of CMS Medicare enrollment to Visit 5 date. Following protocols established in extant studies, we will consider the presence of at least one of the ICD-9 codes listed in Table 1 in any position on the claim (inpatient or outpatient) as a diagnosis of dementia<sup>1,17</sup>. As a beneficiary may have more than one type of dementia, we will construct a person-level file, grouping all dementia diagnoses per cohort member

obtained from claims for care received during the period of observation. In a sensitivity analysis, we will consider an outpatient dementia diagnosis as present if two of the listed codes are present in claims for two consecutive outpatient visits within one year. Given the potentially small sample sizes, we will not differentiate individual dementia subtypes (i.e. Alzheimer's disease, cerebrovascular disease, Lewy Body disease) from the ICD-9 diagnostic codes found in the claims.

Diagnostic coding for MCI has not been well established. In a recent publication, Lin and colleagues used ICD-9 code 331.83 to identify MCI from Medicare claims<sup>18</sup>. We are not aware of any work that would have validated this code against MCI classification and have no evidence of the frequency of its use in clinical practice. We will however examine the presence of this code in the claims preceding ARIC MCI and dementia classification.

| <b>Table 1 Dementia diagnostic codes (ICD-9)</b> |                                                                                                                               |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| <b>Dementia subtype</b>                          | <b>ICD-9 diagnostic codes</b>                                                                                                 |
| Alzheimer's disease                              | 331.0                                                                                                                         |
| Vascular                                         | 290.40, 290.41, 290.42, 290.43                                                                                                |
| Lewy body                                        | 331.82, 332.0, 331.0                                                                                                          |
| Fronto-temporal                                  | 331.1, 331.11, 331.19                                                                                                         |
| Alcohol induced                                  | 291.2                                                                                                                         |
| Other                                            | 046.11, 046.19, 292.82, 333.4                                                                                                 |
| Not otherwise specified                          | 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.9, 294.1, 294.10, 294.11, 294.20, 294.21, 294.8, 331.2, 797 |

**Diagnostic setting:** In the identification of cognitive impairment from ARIC participants Medicare claims' we will use a broad range of claims, including those for inpatient and ambulatory care, home health care, and claims from skilled nursing facilities. Evidence of a dementia-specific code in Medicare claims for any healthcare encounter occurring prior to the Visit 5 date will be considered as positive dementia ascertainment from claims. In secondary analyses, we will partition the claims into 4 categories: inpatient, outpatient, and home health, and skilled nursing facility (SNF) claims, with the latter two types of claims grouped together. In supplemental analyses, we will limit the study population to those enrolled in Part D Medicare (from 2006) and will add to the definition of dementia based on diagnostic codes (pooled from all claim sources) evidence of dementia-targeted prescription medications (cholinesterase inhibitors and memantine).

A limitation in our analyses will be that presence of dementia-specific codes in the claims data will be contingent on study participants having had a healthcare encounter during the period of observation. By considering the full extent of time from Medicare enrollment to Visit 5 date, we will maximize the potential for participants to have had such encounters.

We hypothesize that we will not observe dementia-related diagnostic codes in claims for a large proportion of participants with an ARIC classification of cognitive impairment. That proportion will be greater for participants with an MCI classification as compared to those classified with dementia.

## **Aim 2.**

### **Assessment of comorbidities associated with dementia**

In the attempt to capture the earliest evidence of morbidity and care associated with future cognitive impairment classification we will use ARIC Medicare claims from January 1, 1991 through December 31, 2013 where available based on FFS Medicare enrollment.

We propose to take advantage of the wide range of clinical inpatient and outpatient services represented by the claims to examine the prevalence of diagnostic codes for comorbidities prior to a dementia and MCI diagnosis. Existing studies suggest that difficulty in diagnosing dementia and the prodromal nature of the disease may limit providers' initial use of dementia codes in favor of codes for conditions such as depression<sup>19,20</sup>.

Assessment of the number and type of comorbidities preceding a diagnosis of cognitive impairment (MCI or dementia) will be performed over pre-specified retrospective look-back epochs (6 months, 1 year, 2 years, etc.) from the date of diagnosis. The ARIC syndromic dementia classification was performed only at the time of Visit 5, therefore, the date of dementia and MCI diagnosis cannot be easily obtained from extant ARIC data. For participants with claims-based evidence of cognitive impairment, we will use the first date of the appearance of a dementia (or MCI) ICD9 diagnostic code in the inpatient or outpatient setting as the date of incidence of cognitive impairment. For participants with no claims-based evidence of cognitive impairment and those classified at Visit 5 as having no cognitive impairment, we will use the date of Visit 5 as the index "incident" date. To ensure the capture of all inpatient and outpatient claims, for each look-back period we will require participants' continuous enrollment in FFS Medicare.

The Medicare Provider Analysis and Review (MedPAR) records will be used to identify morbidity from inpatient stays. Carrier claims for new and established office visits, new and established preventive medicine visits, and

consultations (i.e. Evaluation and Management claims) will be used to identify comorbidities diagnosed in ambulatory care. Additionally, Outpatient claims will be used to identify comorbidities associated with care received at the Federally Qualified Health Centers and Emergency Department visits that did not result in a hospitalization. Stays at skilled nursing facilities and home health will be identified from annual SNF and Home Health claims.

### ***Assessment of inpatient and outpatient visits prior to cognitive impairment onset***

Using the date of MCI and dementia incidence, assigned as above, we will examine patterns of healthcare use preceding MCI and dementia diagnosis in pre-specified time periods (6 months, 1 year, 2 years, etc.) . We will document the number and frequency of claims for inpatient and primary and specialty outpatient care (including ED visits and skilled nursing and home health care) among participants classified as having dementia, MCI, or no cognitive impairment.

### ***Machine learning algorithms***

We will use unsupervised machine learning protocols to explore the presence of patterns in morbidities preceding the Visit 5 cognitive impairment ascertainment, comparing patterns of occurrence of morbidities in inpatient and

| <b>Table 2. Comorbidity categories expected from claims</b> |
|-------------------------------------------------------------|
| Neoplasms                                                   |
| Diseases of the blood                                       |
| Endocrine and metabolic disorders                           |
| Mental and behavioral disorders                             |
| Disease of the nervous system                               |
| Ear and eye disorders                                       |
| Disease of the circulatory system                           |
| Respiratory diseases                                        |
| Diseases of the musculoskeletal system                      |
| Renal diseases                                              |
| Fractures, falls, fall risk                                 |

outpatient claims across the cognitive impairment classification categories. We propose that machine learning techniques will allow us to efficiently take advantage of the large amount of information contained in the claims to discover complex patterns of comorbidity and healthcare utilization. Methods developed in this proposal may be applied to future assessments of pre-dementia care and disease patterns from other comprehensive data sources, such as electronic health records. Comorbidities will be identified from ICD9 codes present in the claims. In our initial agnostic approach we will apply the machine learning algorithms to all ICD9 codes identified from the relevant claims. As different codes can refer to the same disease, in subsequent analyses we will group codes according to pre-specified disease categories (Table 2)<sup>10,21,22</sup>.

In a preliminary step, we will assess the separability of the data using the Hopkins statistic and VAT: Visual Assessment of cluster Tendency. We will then apply k-means and hierarchical algorithms to identify clusters of diagnostic codes within the a priori defined time epochs (as above) prior to the diagnosis of cognitive impairment. We will also explore the existence of temporal patterns of morbidity clusters in the time prior to the diagnosis of cognitive impairment.

For k-means cluster analyses we will apply the algorithm over multiple iterations to reduce the likelihood of random results. We will use distance and similarity measures to assess the fit of the model and will examine all results for the presence of outliers. Model generalizability and robustness will be assessed using n-fold cross-validation (exploring different n values). Resulting clusters will be examined with respect to the clinical coherence of component diagnostic codes. We propose to conduct all analyses using machine learning tools available in SAS.

### **Potential study limitations:**

This study will be limited in its generalizability by the reduced representativeness of the ARIC cohort at Visit 5, resulting from selective non-participation in the visit. Further limitation to generalizability and to the power of analyses will be imposed by the strict inclusion criterion of fee-for-service Medicare enrollment at the time of Visit 5. In Table 3, we show the reduction in sample size that will result from the limitation of the cohort to the FFS Medicare enrollees.

We are imposing the restriction to FFS Medicare in order to be able to have complete ascertainment of outpatient events. Managed care organizations have until recently not been required to report to CMS itemized claim information. The claims, especially outpatient claims, for beneficiaries enrolled in managed care are therefore incomplete and do not allow for a comprehensive examination of received care. Our preliminary data, based on ARIC ms#2161 in which we compared mortality and

**Table 3. ARIC Level 1 classification of cognitive impairment at Visit 5, by FFS Medicare status**

| <b>Visit 5 Level 1 classification</b> | <b>Full Visit 5 cohort, N=6,358</b> | <b>FFS Medicare at Visit 5, N=3,639</b> |
|---------------------------------------|-------------------------------------|-----------------------------------------|
| Dementia, N(%)                        | 344 (5.3%)                          | 210 (5.8%)                              |
| MCI, N(%)                             | 1,374 (21%)                         | 766 (21.1%)                             |
| No cognitive impairment, N(%)         | 4,755 (72.7%)                       | 2,627 (72.2%)                           |
| Missing or unknown, N(%)              | 65 (1%)                             | 36 (1%)                                 |

rates of CVD events among Medicare FFS beneficiaries and those in managed care, suggest however, worse outcomes among FFS Medicare, as compared to managed care enrollees. This most likely reflects the selection of beneficiaries with actual costs of care below predicted levels by the capitated managed care programs and limits generalizability of findings to the population of FFS Medicare beneficiaries<sup>23,24</sup>.

**7.a. Will the data be used for non-CVD analysis in this manuscript?** \_\_\_\_ 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?** \_\_\_\_ 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?** \_\_\_\_ 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"?** \_\_\_\_ 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.cscce.unc.edu/ARIC/search.php>**

☒ 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

The ARIC NCS study

**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.cscce.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.csecc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

**13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication.** Approved manuscripts should be sent to Pingping Wu at CC, at [pingping\\_wu@unc.edu](mailto:pingping_wu@unc.edu). I will be using CMS data in my manuscript ☒ Yes ☐ No.

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