ARIC Manuscript Proposal #2542

PC Reviewed: 4/14/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Validation of a Medicare claims-based algorithm to identify frailty among older adults**

b. Abbreviated Title (Length 26 characters): **Claims-based frailty in ARIC**

2. Writing Group:

Writing group members: Jennifer Lund, Anna Kucharska-Newton, Priya Palta, Anne-Marie Meyer, Kim Faurot, Til Stürmer, Michele Jonsson-Funk, Beverly Gwen Windham, Karen Bandeen-Roche (has been invited to participate), Lisa Pompeii, Michael Griswold

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

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3. Timeline: We plan to submit an abstract based on this proposal to the American Geriatrics Society Annual Scientific Meeting (abstracts due December 5, 2015). Manuscript submission is planned for Spring 2016.

4. Rationale:

Frailty is a geriatric syndrome characterized by decreased physiological reserve and resistance to stressors causing an individual to become more vulnerable to adverse health outcomes. The most widely accepted definition of frailty was first operationalized by Fried and colleagues using data from the Cardiovascular Health Study (CHS).[1] The co-occurrence of multi-system, age-associated declines is the impetus for defining frailty as a clinical phenotype that includes the presence of three or more of five characteristics: (1) unintentional weight loss, (2) weakness, (3) exhaustion, (4) decreased physical activity and (5) slowness.[1] The CHS-defined frailty phenotype has been used to describe frailty in several cohorts of community-dwelling older adults.[2-5] Using the CHS-defined frailty phenotype, members of this manuscript proposal team are using extant Visit 5 data to estimate the prevalence of frail, pre-frail and robust frailty states within the ARIC Study cohort (ARIC ms #2465– Kucharska-Newton et al) and examine the associations between frailty and related adverse outcomes (e.g. falls, physical health, mental health, and all-cause mortality).

Administrative claims data are frequently used in epidemiological analyses; however, these data are limited in their capture of multiple health domains due to their inherent structure and reliance on billing-related codes and standardized nomenclatures to identify diagnoses, procedures, treatments and medical equipment. Using data from the Medicare Current Beneficiary Survey (MCBS), a nationally representative sample of Medicare Beneficiaries,[6] Faurot and colleagues (also members of the writing group for this manuscript proposal) recently developed and internally validated an administrative claims-based algorithm to predict dependency in activities of daily living (ADL),[7] such as bathing and dressing.[8] Faurot[7] defined ADL dependency (ADL-D), a marker of advanced functional decline, as: 1) having some difficulty with at least one ADL and 2) reporting the need for help from another person to complete the activity or being unable to complete the activity because of their health. The prevalence of ADL-D was 9.5% among the cohort and the strongest claims-based predictors of ADL-D included claims for home hospital bed (OR=5.44, 95% CI: 3.28–9.03) and wheelchair (OR=3.91, 95% CI: 2.78–5.51). The final predictive model had a c-statistic of 0.845 and when categorized (predicted probability of ADL-D $\geq$20% vs. <20%) was strongly associated with an increased risk of death (adjusted hazard ratio=3.19, 95% CI: 2.78, 3.68).

These analyses are promising; however, they are based on a marker of frailty (i.e., ADL-D) instead of the phenotype itself and need to be further validated in external and contemporary cohorts. We therefore propose to examine the performance of the algorithm derived by Faurot and colleagues with respect to the prediction of the ARIC cohort-defined frailty construct. The ARIC study presents a unique opportunity to examine the validity of a frailty model based on administrative claims data and evaluate its association with longitudinal outcomes from both the cohort and claims data. Such a model would be useful in a variety of research contexts, where information related to multiple health domains including functional status is unavailable (e.g., administrative claims databases that are not linked to cohorts).

5. Main Hypothesis/Study Questions:
Specific aims of this study are to use data obtained during ARIC Visit 5 and the semi-annual follow-up interviews as well as the linked CMS Medicare fee-for-service claims data to:

Aim 1: Examine the validity of the Faurot Medicare claims-based algorithm to categorize study participants as frail or non-frail using the ARIC cohort-defined frailty construct (further described below) as the gold standard.

- Assess the goodness of fit or calibration of the existing claims-based model by comparing the observed frailty phenotype vs. the predicted frailty phenotype using Hosmer-Lemeshow tests as well as the Pearson's chi-square test.
- Evaluate the discriminative ability of the existing claims-based algorithm to identify frailty using receiver operating curve (ROC) analyses. Compare with Faurot ROC curves obtained from a different sample of CMS Medicare claims in 2006.
- Determine the reliability of the final model by grouping ARIC participants into quantiles according to their predicted probability of claims-based frailty and plot the proportion of individuals with ARIC cohort-defined frailty for each quantile.
- Compare the coefficients for the 23 variables included in the original Faurot analysis used to predict ADL-D to the coefficients that result when using the same 23 variables to predict ARIC cohort-defined frailty in the ARIC cohort.

Aim 2: Prior studies[9] have shown that preventive medications are selectively prescribed to healthy, robust older adults and withheld from those with shorter life expectancies (i.e., frail). Using this information, we will seek to improve upon the existing claims-based frailty prediction model (from Aim 1) to better differentiate non-frail from frail individuals by incorporating this selective prescribing behavior using data from: 1) the ARIC cohort Visit 5 interview and 2) Medicare Part D claims. Glynn et al[9] identified a number of drug classes (lipid-lowering agents, nonsteroidal anti-inflammatory agents, beta blockers, thiazides, glaucoma drugs, calcium channel blockers, and anti-anxiety drugs) which will serve as the basis for our inquiry.

Our primary analysis will utilize the ARIC cohort Visit 5 interview data to capture medication use and evaluate the incremental predictive benefits of adding prescription medications to the Medicare claims-based frailty model. However, as most epidemiologic analyses using claims will not have interview data on medications, we will also run analyses within a subset of ARIC study participants with Medicare fee-for-service Parts A, B and Part D coverage. We will describe differences in demographic and other individual characteristics between these two study populations. Specifically, we will:

- Assess the goodness of fit or calibration of the new claims-based model including medications by comparing the observed frailty phenotype vs. the predicted frailty phenotype using Hosmer-Lemeshow tests as well as the Pearson's chi-square test.
- Evaluate the discriminative ability of the new claims-based algorithm with medications to identify frailty using receiver operating curve (ROC) analyses. Compare with Aim 1 ROC curves.
- Determine the reliability of the final model by grouping ARIC participants into quantiles according to their predicted probability of claims-based frailty and plot the proportion of individuals with ARIC cohort-defined frailty for each quantile.

Aim 3: To test the concurrent and predictive ability of the models in both Aims 1 and 2, we will evaluate the relationship between the claims-based frailty measures and a number of outcomes. Each of the models in Aims 1 and 2 will generate a predicted probability for each individual in the ARIC cohort, meeting all study eligibility criteria. By applying relevant cut-points similar to those used by Faurot et al (i.e., <5%, 5-<10%, 10-<20%, 20-<40%, 40%+), we will estimate associations between the predicted claims-based frailty categories and related outcomes (e.g. changes in perceived physical and mental health, falls, physical ability and all-cause mortality) using both ARIC cohort and Medicare data.

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: Analyses will be conducted using information obtained during ARIC Visit 5 (n=6538) and the Medicare enrollment and claims data for the relevant study period. Excluded from analyses will be study participants with missing information on all 5 component characteristics defining frailty (n=41) and those participants who do not have 12-months of continuous enrollment in Medicare Part A and B (fee-for-service eligibility) prior to the Visit 5 interview date (n=3033), resulting in a cohort of approximately 3504 individuals. A sub-analysis of Aim 2 will further exclude individuals who do not have 12-months of continuous Medicare Part D enrollment prior to the Visit 5 interview date. For claims-based outcomes in Aim 3 (with the exception of mortality), individuals will be censored when they disenroll in Medicare fee-for-service Parts A and B, as we would be unable to capture study outcomes in this situation.

Definition of frailty in ARIC: The ARIC Study Coordinating Center in collaboration with members of the ARIC Physical Function/Aging working group has created a frailty variable based on the a widely accepted frailty construct, developed initially by Fried et al on the basis of data collected in the Cardiovascular Health Study.[1] Component elements of the frailty construct were ascertained at ARIC Visit 5, with the exception of weight loss which was calculated from visit 4 data (Table 1 below). For all analyses, we will dichotomize individuals as frail, defined as having 3+ frailty components present or non-frail (collapsing individuals defined as robust and pre-frail), defined as having <3 frailty components. Preliminary data indicate that among eligible individuals, 7% and 93% will be considered as frail and non-frail, respectively.

Table 1. Operationalization of the frailty construct in ARIC cohort

Characteristics of frailty	**Definition**
Unintentional weight loss	10 percent of unintentional weight lost from V4 to V5 or BMI<18.5 at Visit 5
Low energy expenditure	Gender-specific 20th percentile rank of the Baecke leisure sports activity index
Low walking speed	Gender- and height-adjusted time in seconds used to walk 4 meters. Slowest speed will be defined as the 20th percentile of the distribution.
Low level of physical energy (Exhaustion)	Responded "some of the time" or "most of the time" to either of the following CESD questions: CES3 (*I felt everything I did was an effort*) or CES11 (*I could not get "going"*)
Low grip strength	Gender- and BMI- specific grip strength in the lowest 20% percentile of distributions

Medicare claims-defined frailty: We will use the coefficients from the final model defined by Faurot and colleagues and apply them to the Medicare claims for individuals fulfilling the study eligibility criteria. **Supplemental Table 1** below includes the administrative codes (based on the International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9) diagnosis and procedure codes as well as Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPC) codes) and coefficients included in the final model.

Medications that may improve claims-based prediction of frailty: Within the two cohorts (i.e., the 1) ARIC cohort with interview-based medication data and 2) the Medicare Part D cohort) we will identify the top 20 most commonly used/dispensed medication classes and evaluate whether including information about these medications improves the claims-based prediction of frailty in the ARIC cohort. We will compare the improvement in claims-based prediction from our primary approach (using the most prevalent medication classes) to a secondary approach using the 20 drug classes evaluated by Glynn and colleagues (which were also based on prevalence in a different population), which demonstrated strong relationships with short-term mortality, likely due to their associations with frailty and not the underlying effect of the drug.[9] Analyses that include subsets of these 20 drug classes will also be considered.

Outcomes: To evaluate the concurrent and predictive criterion validity of the claims-based frailty model, we will use clinical expertise to select cut-points and evaluate the associations between the predicted probability of frailty based upon the claims and the outcomes listed below.

Concurrent and longitudinal associations (concurrent and predictive frailty criterion validity): We will apply methods developed for the assessment of the ARIC frailty construct to examine the validity of the claims-based frailty variable. We will examine concurrent and longitudinal associations of the predicted probability of frailty derived from claims with the following outcomes (detailed further in **Figure 1** below):

- Change in perceived physical and mental health status. The SF-12 questionnaire was administered to study participants at the time of Visit 5 and during the GNC semi-annual follow-up interview (administration period 01/2014-03/2015). We will take advantage of the availability of repeat SF-12 measures to examine the association of claims-based frailty with change in these composite quality of life measures. The composite physical and mental health SF-12 scores exist as ARIC study derived variables.
- Risk of falls. Questions concerning falls were administered to the study participants during the GNB semi-annual follow-up interview, which was conducted from 01/2013 through 03/2014. At that time participants were asked about falls and number of falls in the previous 6 months. We will examine the association of claims-based frailty with the incidence of falls.
- Physical ability: The ability of study participants to perform *selected* ADLs and instrumental ADLs was ascertained through the physical ability questionnaire which was administered at the time of the GEN and the GNB semi-annual follow-up interviews (administration periods: 01/2012-03/2013 and 01/2013-03/2014, respectively). We will examine the association of claims-based frailty with physical ability at both time periods and as a change in physical ability occurring during the intervening year.
- All-cause mortality: As the goal of this analysis is focused on the use of administrative claims data, we will obtain mortality data primarily from Medicare enrollment files (through 2013). Further data on death may be obtained from the Annual Follow-up interviews, death certificate data and the National Death Index.

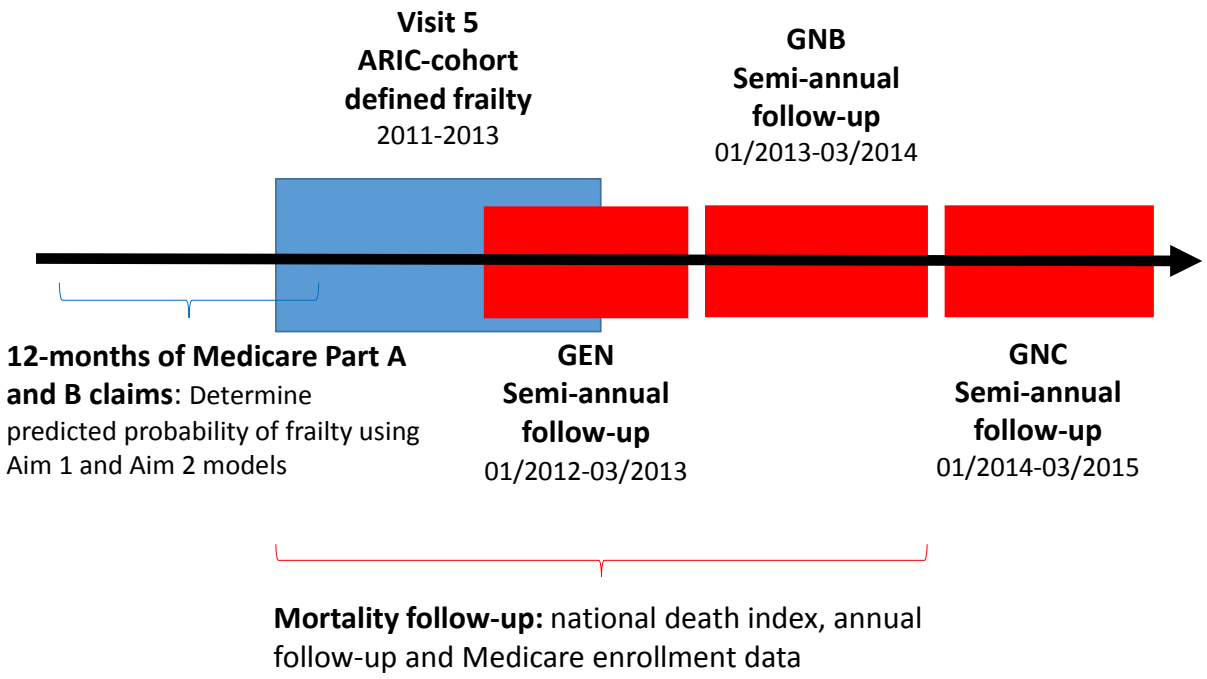

Figure 1. Study design schematic for the validation of a Medicare claims-based algorithm to identify frailty among older adults. Markers in blue denote the measurement of frailty (cohort and claims-based measures) and markers in red denote the concurrent and longitudinal outcomes that we will evaluate in Aim 3.

Supplemental Table 1. Medicare claims defined indicators of frailty and coefficients from the predictive model of activities of daily living dependences (ADL-D)

Variable	Coefficient from the predictive model	ICD-9 diagnosis, CPT and HCPCS codes
Intercept	-3.6954	
Age (centered at 65)	-0.00139	
Age squared	0.00207	
African-American	0.2776	
Hispanic/Latino	-0.5071	
Other race	0.8581	
Female gender	0.3199	
Ambulance	0.4007	A0426, A0427, A0428, A0429, A0999
Hospital Bed	1.692	E0250,E0251,E0255, E0256, E0260, E0261, E0265, E0266, E0270, E0290, E0291, E0292, E0293, E0294, E0295, E0296, E0297, E0301, E0302, E0303, E0304, E0316
Oxygen	0.7836	E1390, E1391, E1392,E0431, E0433, E0434, E0435, E0439, E0441, E0442, E0443
Wheelchair	1.3585	E1050, E1060, E1070, E1083 E1084 E1085 E1086 E1087 E1088 E1089 E1090 E1091 E1092 E1093, E1100, E1110, E1120, E1140, E1150, E1160, E1161, E1170, K0001 K0002 K0003 K0004 K0005 K0006 K0007 K0008 K0009
Bladder dysfunction	0.337	783.3x, 788.2x, 596.5x, 599.6x
Stroke/Brain injury	0.4691	349.82, 433.01, 433.11, 433.21, 433.31, 433.91, 434.01, 434.11, 434.91, 436, 348.x, 430.x, 431.x, 432.x, 852.x, 853.x, 854.x
Coagulopathy	-0.7251	286.6, 286.7, 286.9, 287.4, 287.5
Skin ulcer	0.4157	707.x
Dementias	0.6897	290.x, 294.x, 331.x, 333.90, 333.92, 333.99, 780.93, 438.0, 797
Difficult walking	0.397	781.2, 781.3, 438.85, V46.3, 719.7x
Complications of diabetes mellitus	0.3877	250.4x, 250.6x, 250.7x, 250.9x
Heart Failure	0.411	428.x, 425.x, 429.0, 429.1, 429.3, 429.4
Arthritis	0.2835	711.x, 715.x, 718.x, 719.0x, 719.1x, 719.4x, 719.5x, 719.9x, 716.5x, 716.6x, 716.8x, 716.9x
Lipid abnormality	-0.4291	272.x
Paralysis	1.5122	438.2x, 438.3x, 438.4x, 438.5x,781.4, 342.xx, 344.xx
Parkinson's disease	1.1034	332.x
Podiatric care	0.4304	700.x, 703.x, 681.1x

Psychiatric	0.5308	29x.x, 310.x, 300.0x, 311
Rehabilitation	-0.5103	V57.1, V572.1, V57.3, V57.9, V57.8x
Cancer screening	-0.5085	V76.x
Sepsis	0.4559	01x.x,031.0, 031.2, 790.7, 112.81, 112.83, 112.5, 032.82, 032.83, 053.13, 136.3, 785.4, 053.0, 054.5, 036.x, 038.x, 041.x, 681.x, 682.x, 730.x, 320.x, 321.x, 040.0x
Vertigo	-0.5217	386.x, 780.4
Weakness	0.3566	728.2, 728.87, 799.3, 728.2, 728.3, V49.84

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 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 __ x __ 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.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)?
ARIC mp#13030 Godino J. et al. "Diabetes, hyperglycemia, and the burden of frailty syndrome in the Atherosclerosis Risk in Communities Study".

ARIC mp#2465 Kucharska-Newton et al. "Operationalizing frailty in the ARIC cohort".

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/

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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