ARIC Manuscript Proposal #4058

PC Reviewed: 5/17/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Proteomic aging clock and quality of life

b. Abbreviated Title (Length 26 characters): Proteomic clock and QOL

2. Writing Group:

Writing group members:

Patricia Jewett, Anna Prizment, Anne Blaes, Shuo Wang, Weihua Guan, Elizabeth Platz, Corinne Joshu

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **PJ [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: Analyses will begin within immediately after approval and will be finished within 12 months of study begin.

4. Rationale:

The proposed analysis will build on an analysis conducted by doctoral candidate Shuo Wang (see section 9 below) under the supervision of Dr. Prizment and statistician Dr. Guan who have constructed a novel proteomic aging clock based on proteins measured by Somascan at Visit 2, 3, and 5 in ARIC data. The “proteomic aging clock” at each visit combines a set of proteomic-based aging-related biomarkers as a surrogate estimator of biological age. In their analyses, Ms

Wang and Dr. Prizment have shown that proteomic age is highly correlated with chronological age in healthy people and is associated with mortality, suggesting it is a surrogate measure of biological age (findings not yet published).

Beyond its immediate potential use in biological application, it is unknown whether the proteomic is related to quality of life (QOL). Previous studies have established associations between chronological age and QOL,[1-3] but whether associations are similar or different in relation to biological age remains unknown. QOL is a multidimensional construct, including domains of physical, psychological, social health, and overall life satisfaction;[4] and it is a recognized major health outcome in cancer with impacts on prognosis, treatment adherence, and survival.[5-7] QOL is important to cancer patients and matters equally, if not more than, length of life.[8] The number of cancer survivors is growing as the population ages, and understanding QOL in this population, is crucial in order to meet the needs of this population.[9] If QOL is associated with proteomic age or changes in proteomic age, then proteomic age could be used as a clinical indicator for interventions targeted at mitigating potential threats to QOL in those who live with cancer, for example by referring patients to mental health or social services or counselors.

We will use the SF-12, a validated and established instrument used in the ARIC study to measure QOL.[10] The SF-12 questionnaire, a short form of the SF-36, assesses health-related QOL and has been validated. It consists of 2 subscores for physical and mental health-related QOL which each cover 4 domains: physical functioning, role-physical, bodily pain, and general health (self-graded health status); mental health, role-emotional, social functioning, and vitality. Each item is scaled on a scale between 1 and 5, with higher scores indicating better QOL. We will evaluate scores using standard methods: a raw QOL score for each domain is calculated as the sum across all relevant items. A final score for each domain between 0 and 100 is calculated which can be further standardized to general US population scores with a mean of 50 and a standard deviation of 10.

As secondary outcome, we will assess depression in relation to proteomic age. Individuals with cancer experience increased prevalence of depression.[11] For this, we will use the CES-D Short Form that has been used in ARIC at V5 and V6 and which includes 11 items selected from 20 original items that define the full CES-D Form. This short-form CES-D demonstrates good validity.[12] Each item is scored on a scale between 0 and 2 (0=hardly ever or never; 1=some of the time; 2=much or most of the time) for each item, such that the total CES-D score ranges between 0 and 22. We will also evaluate a CES-D cutoff score of 9 or greater that has been applied in previous ARIC work.[13]

The relationship between aging, depression, and quality of life are likely complex: a U-shaped curve of depression by chronological age[14] has been described (relatively higher depression levels at younger and very high ages). Depression is also associated with cognitive function[15-17] and often co-occurs with dementia; but the direction of these associations is uncertain and possibly multidirectional, i.e. depression may be a potential consequence, risk factor, or a prodrome of dementia, or several or all of these.[18, 19] It is possible that depression is a mediator or an effect modifier in the relationship between aging and QOL; therefore, we will use

various statistical models (including interaction tests) to investigate the relationships between aging, depression, and quality of life.

In our analyses, we will cross-sectionally relate proteomic age to QOL a) among cancer survivors at Visit 5, and b) among individuals who had not been diagnosed with cancer at V5. We are particularly interested in those with cancer; but also hypothesize that proteomic age may be related to QOL in the general population. By running this analysis stratified in these 2 population, we will be able to assess potential differences in the associations between proteomic age and QOL (interaction with cancer status).

5. Main Hypothesis/Study Questions:
The overall goal of this study is to measure the associations between and QOL (primary outcome) and depression (secondary outcome) and the predictors a) proteomic age (adjusted for chronological age), b) proteomic age acceleration, and c) changes in proteomic age.

H1: Higher proteomic age, after adjustment for chronological age, is cross-sectionally associated with a)lower QOL (measured as several subscores) and b) higher prevalence of depressive symptoms in those with and without cancer.

H2 and H3: Analogously, Proteomic age acceleration and large (compared with average) increases in proteomic age are associated with lower QOL and higher prevalence of depressive symptoms.

H4: The above associations may differ in those vs. without a prior cancer diagnosis; for example because of cancer treatments and other unknown/unmeasured biological differences between these populations. If such differences in these associations exist, we expect the association to be stronger among cancer survivors compared to those without a personal history of cancer.

Sensitivity analysis: In a prospective analysis, we will examine if higher proteomic age is associated with lower QOL assessed at V6.

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:
Group 1: cancer survivors (those with prevalent cancer at V5 who had a cancer diagnosis [except non-melanoma skin cancer] at least a year prior to their V5 visit).

Group 2: Anyone without a personal history of cancer at their V5 visit.

Main outcomes:
- QOL based on the SF-12 instrument; measured at ARIC at V5 and V6.
- Depression based on the CES depression form; measured at ARIC at V5 and V6.

Standard methods will be used to evaluate the continuous SF-12 scores (mental and physical QOL SF-12 subscores as well as the total SF-12 scores); and the CES depression scores.

Main exposure:
Model a: Proteomic aging clock; calculated in ARIC at V5; continuous age score
Model b: Age acceleration of proteomic age at V5; continuous acceleration score
Model c: Change in proteomic age (proteomic age at V5 minus proteomic age at V2; continuous change score)

Covariates:
Covariates in models a, b, and c among individuals both with and without cancer:

- Sex
- Income
- Education
- Race
- ARIC study center
- marital status
- possibly: eGFR
- In the model with proteomic age scores as the predictor we will additionally adjust for chronological age.

Additional covariates in model among those with cancer:

- Cancer stage
- Time since cancer diagnosis
- Cancer type

Additional sensitivity analyses will

- include the following covariates which could be either confounders or mediators the cross-sectional analysis: BMI, physical activity, smoking status, comorbidities
- Stratified analyses by gender to see if the observed associations differ by sex (potential effect modification).

Statistical analysis:
We will run descriptive statistics (means, standard deviation, frequencies) and linear regression analyses, with (continuous) proteomic age (second model: age acceleration; third model: change in proteomic age between V2 and V5) as main exposure, and (continuous) SF-12 QOL and CES depression scores as outcomes (total scores as well as physical and mental health subscores on the SF-12 instrument); unadjusted and adjusted for the above described covariates. Proteomic age, age acceleration, changes in proteomic age since V2, SF-12, and CED depression scores will be used cross-sectionally from the same ARIC visit (V5). Time-independent covariates (sex, race, study center; cancer characteristics at the time of diagnosis) will be taken from baseline or the survey when they were measured, time-variant covariates (BMI, smoking, physical activity, comorbidities) will be used from V5 if possible; otherwise from other earlier visits.

To evaluate the proportion of participants with CES-D scores of 9 or greater, we will use Chi-squared tests and adjusted logistic regression as appropriate.

As a robustness check, we will rerun the main model using QOL and depression outcomes measured at V6 (proteomic age [acceleration] measured at V5) to see in the prospective analysis if associations hold if QOL and depression are measured 4-5 years after measurement of proteomic age. To account for non-response bias (missing QOL and depression values at V6), we will use inverse probability weighting.

Power calculation:
Assumptions:
- sample size N=1,000 individuals with prevalent cancer at V5 who completed the SF-12
- small effect size (standardized effect size value 0.14) of the association between proteomic age predictors and SF-12
- 25 degrees of freedom in the linear regression analysis used up by covariates

➔ Estimated power=70%

➔ This power will be greater in the analysis among individuals without cancer (sample size > 1000)

Anticipated limitations / challenges:
- Cross-sectional analysis: no causal inference possible. The power for the prospective analysis (proteomic age measures from V5; SF-12 and CES-D measures from V6) may be limited because participants age getting older, getting sick, and some have not answered V6 questionnaire (6,500 total observations at V5 vs. 4,000 total observations at V6)
- Potential unmeasured confounding among those with cancer: unknown treatment status (currently treated vs. not) at the time of survey; type of treatment received; caregiver status

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

8.a. Will the DNA data be used in this manuscript?
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/aricproposals/dtSearch.html

X Yes No

Our proposal does not overlap with the scope of previous proposals, but builds on previous proposals related to developing the proteomic aging clock in ARIC (proposals by Wang and Prizment)

Manuscript Proposal #: 3739
Manuscript Proposal Title: Proteomic age acceleration and cancer incidence: The Atherosclerosis Risk in Communities Study

Manuscript Proposal #: 3848
Manuscript Proposal Title: Proteomic age acceleration and mortality in cancer survivors: The Atherosclerosis Risk in Communities Study

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)?

See cited proposals in the section above.

We will use similar outcomes as these studies:

Wu, Aozhou, Josef Coresh, Elizabeth Selvin, Hirofumi Tanaka, Gerardo Heiss, Alan T. Hirsch, Bernard G. Jaar, and Kunihiro Matsushita. "Lower extremity peripheral artery disease and quality of life among older individuals in the community." Journal of the American Heart Association 6, no. 1 (2017): e004519.

Sonsin-Diaz N, Gottesman RF, Fracica E, Walston J, Windham BG, Knopman DS, Walker KA. Chronic Systemic Inflammation Is Associated With Symptoms of Late-Life Depression: The ARIC Study. Am J Geriatr Psychiatry. 2020 Jan;28(1):87-98.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? X **Yes** **____ No**

AS1995.04 Cancer Study

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
X **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.

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