

## Manuscript Proposal #3739

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**1.a. Full Title:** Proteomic age acceleration and cancer incidence: The Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters):** Proteomic age acceleration and cancer risk

### 2. Writing Group:

Writing group members: Shuo Wang, Anna Prizment, Elizabeth Platz, Sithara Vivek, Bharat Thyagarajan, Anne Blaes, Jim Pankow, Weihua Guan (authorship order TBD and other ARIC researchers are welcome to participate).

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

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**3. Timeline:** Analyses will begin within one year after approval.

**4. Rationale:**

In this study, we propose to examine the association between proteomic age acceleration and risk of cancer overall and by subtypes. We have an ancillary proposal (AS2020.32) entitled “Proteomic Aging Clock and Colorectal Cancer” approved in ARIC.

Aging plays a critical role in cancer, as indicated by an increasing incidence of most cancer types with age.<sup>1,2</sup> This could be explained by the accumulation of random genetic mutations and epigenetic alterations, weakened immune system and malfunction of repair processes in aging individuals.<sup>3-6</sup> Also, growing evidence shows that individuals with cancer age faster than those without cancer (so called accelerated aging).<sup>7</sup> However, it is not clear how much rate of aging differs between those with and without cancer, and whether this difference starts even before the cancer is diagnosed. These issues may be examined using aging clocks, which are a set of molecules capable of predicting individual’s age. Aging clocks can provide specific information about how old an individual is biologically, independent of the chronological age.<sup>8</sup> Examining the aging clocks in cancer is especially important because most cancer cases develop over a long period of time and have a long subclinical period, and 30%-50% of all cancer cases are preventable;<sup>9</sup> thus, the aging clock could provide a new method for identifying people at high risk of cancer that need more frequent screening or treatment with anti-aging agents, such as metformin.

Several aging clocks have been created, and the most acknowledged among them is epigenetic clock,<sup>10, 11</sup> a set of DNA methylation-based biomarkers in blood or tissue. Epigenetic clock has been shown to be an accurate molecular correlate of chronological age in humans that may predict several health outcomes, including cardiovascular, cancer, and mortality,<sup>12-14</sup> although the underlying mechanism of the age-associated DNA methylation remains unclear.<sup>15</sup>

Several studies examined the epigenetic clock in relation to the incidence of cancer, including overall cancer and cancers of lung, breast, colorectum and pancreas.<sup>14, 16-20</sup> The Normative Aging Study (N = 442) found that an incorporated Hannum and Horvath age acceleration was associated with overall cancer (38 prostate, 50 skin, and 44 other) [HR (95% CI)= 1.06 (1.02,1.10)].<sup>20</sup> The Women’s Health Initiative study (N = 2029) found a one-year increase in Horvath<sup>11</sup> and PhenoAge<sup>14</sup> clocks were statistically significantly associated with a 50% ( $p = 3.4 \times 10^{-3}$ ) and 5% ( $p = 0.031$ ) increase in risk of lung cancer, respectively,<sup>14, 16</sup> while in the Sister Study (N = 2764), Hannum,<sup>10</sup> Horvath, and PhenoAge age accelerations were statistically significantly associated with increased breast cancer risk with the strongest association observed for PhenoAge: HR (95% CI) = 1.15 (1.07, 1.23).<sup>18</sup> However, previous findings were inconsistent regarding colorectal cancer (CRC) and pancreatic cancer risk when using different epigenetic clocks.<sup>17, 19, 21</sup> For instance, EPIC-Italy study (N = 845) found an increased CRC risk in male associated with Horvath ( $P = 0.042$ ) and FHL2 ( $P = 0.036$ ) clocks, but not Hannum, Weidner, or ELOV2.<sup>19</sup> A pooled analysis of Nurses’ Health study, Physician’s health study, and the Health Professionals Follow-up Study (N=824) found positive dose-response trends of Hannum and PhenoAge age accelerations with pancreatic cancer risk with a stronger association observed for Hannum: Q4 vs. Q1: OR (95% CI) = 1.73 (1.11, 2.71), however, for Horvath age acceleration, the highest OR was found in the third quartile compared to the lowest quartile.<sup>17</sup> In summary, epigenetic clock showed associations with different types of cancer but the magnitude of associations depend on the cancer type and the clock used in the study. It is possible that

inconsistencies may be partially explained by the use of different type of clock and the small samples size of the studies.

Recently, “proteomic aging clock”, which combines a set of proteomic-based aging-related biomarkers, has been proposed to be a potential biological age estimator. The proteomic-based biomarker may be a promising alternative biomarker because it, as intermediate phenotype, can reveal direct information on biological pathways that are involved in many of the physiological and pathological manifestations of aging.<sup>22, 23</sup> Using plasma to build a clock is advantageous because plasma proteins are easily measurable in a non-invasive way. Previous laboratory studies found that exposing young mice to plasma from old mice was sufficient to accelerate brain aging in young mice,<sup>24</sup> and exposing aged mice to plasma from young mice could improve their cognitive function.<sup>25</sup> The findings from those studies support the notion that “plasma proteome harbors key regulators of aging.”<sup>26</sup> To our knowledge, there have been no studies that examined proteomic aging clock in relation to cancer.

In this proposed study, we will construct a new proteomic aging clock using ~5000 blood proteins that measured by SomaScan. These proteins have been measured at 1993-1995 (Visit 3, N=11,340) and 2011-2013 (Visit 5, N=6538) and will be measured at 1990-1992 (Visit 2, N=12,589). A previous ARIC study has shown an excellent precision in the SomaScan assay.<sup>27</sup> The ARIC study provides a unique opportunity to examine associations between proteomic-based aging biomarkers and cancer risk because it has already measured SomaScan biomarkers at several time points. This will allow us to use different approaches to build proteomic aging clocks based on the cross-sectional association with age (a standard approach) and based on the change in aging biomarkers levels within the individuals (more novel approach). The availability of well-characterized repeated data on main risk factors for cancer such as body mass index (BMI) and smoking will allow us to examine the impact of aging clock beyond the existing risk factors.

This proposal is the first proposal in the series of proposals about proteomic age acceleration and cancer. Our next proposal will examine the role of age acceleration after cancer diagnosis and compare the association between proteomic age acceleration and mortality among individuals with and without cancer.

Of note, if the proteins from Visit 2 is not available, we will use the proteins from Visit 3 and Visit 5.

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

The goal of this study is to determine the contribution of proteomic age acceleration to the risk of cancer in the ARIC study.

*Hypothesis: A higher proteomic age acceleration is associated with an increased risk of overall cancer and specific cancer types.*

**Specific Aim 1.** Create and validate proteomic aging clock in one-half of randomly selected cancer-free participants in ARIC.

SA1a. Create proteomic aging clocks.

We will create four different clocks based on four panels of proteins, respectively. The proteins in each panel will be chosen in the following way: proteins with largest intra-individual changes in blood levels between Visits 2 and 5 (Panel 1), proteins associated with chronological age in a cross-sectional analysis (Panel 2), or the two panels of age-related proteins proposed in the latest systematic review (Panels 3 and 4). Proteomic aging clock will be created as one value for each individual.

SA1b. Validate each of the proteomic aging clocks created in SA1a.

**Specific Aim 2.** Determine the association between the pre-diagnostic proteomic age acceleration and the risk of overall cancer and specific cancer types

SA2a. Determine the association of the pre-diagnostic proteomic age acceleration with the risk of overall cancer and most common cancers (lung, breast, colorectal, and prostate cancers)

SA2b. Determine the association between the pre-diagnostic proteomic age acceleration and the risk of obesity-related cancer (breast, colorectal, endometrial, ovarian, kidney, pancreatic cancers, liver cancer, and lethal prostate cancer) and smoking-related cancer (lung, pancreatic, esophageal and bladder, stomach, liver, cervical, and kidney cancers).

<b>Specific Aim 1</b>		<b>Specific Aim 2</b>
Study population		Study population
Stage A: Selection of training set	We will randomly select half of cancer-free participants at visit 5 and the same group of participants at Visit 2. The group of cancer-free participants from visit 2 will be used as a training set and the same group of cancer-free participants from visit 5 will be used as validation set.*	The remaining cohort (after taking out half of cancer-free participants (the training set)) at Visit 2, and who have the measurement of proteins at Visit 2 using the SomaScan assay.
Stage B: Creation of proteomic aging clock creation	Same group of people as in the training set.	
Stage C: Validation of proteomic aging clock validation	The randomly selected half of cancer-free participants from visit 5 at stage A will be used as validation set.	

\*Of note, we assume chronological age is a surrogate marker for the proteomic clock in cancer-free participants. We randomly choose the cancer-free participants at Visit 5 first and then go back to choose the same group of participants visit 2 because this can make sure participants in both training set and validation set are cancer-free. We can also randomly choose one-half of all ARIC cancer-free participants, and then we will randomly split those participants into two equally sized groups. The first group will be used as a training set and the second as a validation set.

**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).**

**Inclusion criteria:** The analytic sample will include participants who were free of cancer at baseline (Visit 2), who gave consent to participate in non-CVD research, and who have the measurement of proteins at Visit 2 using the SomaScan assay.

**Exposure:** Circulating levels of proteins will be extracted from the SomaScan assay (v.4) (SomaLogic company).<sup>28, 29</sup> Using this assay, the ARIC study has recently measured more than 5000 plasma proteins in frozen plasma samples collected at Visit 3 (1993-1995, N=11,340) and Visit 5 (2011-2013, N=6538) (Median CV range across ~5 proteins measured from ARIC visit 3 samples: 6.9 – 8.3%). These proteins will be measured using SomaScan at Visit 2 (1990-1992, N=12,589). The proteins constituting the proteomic aging clock will be assessed at baseline (Visit 2) and updated at (Visit 3 and Visit 5, where appropriate). Of note, for those with cancer, only proteins measured before cancer diagnosis will be examined. In all the analysis, we will use the log transformed values of proteins.

**Outcome:** Cancer incidence was ascertained through 2015 using state Cancer registries in Minnesota, North Carolina, Maryland, and Mississippi, and supplemented by abstraction of medical records and hospital discharge summaries.<sup>30</sup> We will follow participants from Visit 2. A total of 4,407 incident cancer cases were ascertained over a maximum follow-up of 25.9 years (until 2015).

**Other covariates of interest:** Demographic and clinical variables of interest such as chronological age, sex, race, education, BMI, collected at baseline, and updated as needed during follow-up will be extracted. Cancer risk factors, such as smoking status, cigarette years of smoking, alcohol use/intake, physical activity, and diabetes, will also be extracted at Visit 2 and other Visits. Information about estimated glomerular filtration rate (eGFR), use of NSAIDs, and hormone therapy will also be extracted.

**Statistical analysis**

**Specific Aim 1.** Create and validate the proteomic aging clock in cancer-free participants in ARIC.

We propose four panels of proteins constituting the clocks. We will create four different proteomic aging clocks based on four protein panels, respectively.

Creating and validating proteomic clock will consist of three stages:

**Stage A.** develop the panel (for panels 1 and 2)

**Stage B.** create the proteomic aging clock (which will have one value for each individual)

**Stage C.** validate the proteomic aging clock

**Panel 1:** We will develop this panel by determining proteins with largest intra-individual changes in blood levels over ~20 years of follow-up among ARIC cancer-free participants (between Visits 2 and 5).

To do this, we will randomly choose one-half of all ARIC cancer-free participants at Visit 5 and then choose the same group of participants from Visit 2. The group of cancer-free people at visit 2 will be used as a training set for selecting the proteins and creating the clock, and the same group of people at Visit 5 will be used as validation set.

Of note, we choose cancer-free participants to develop a proteomic clock because we assume chronological age is a surrogate marker for the proteomic clock in cancer-free participants. We choose cancer-free participants to build a clock because our goal is to identify a clock that will tell us specifically about aging as a risk factors of cancer. We may conduct a sensitivity analysis by building a clock in healthy people and compare with the results with the clocks developed by cancer-free participants. People may be considered healthy if they are absent of any chronic disease (with the exception of controlled hypertension) and cognitive or functional impairment.<sup>22</sup> We randomly choose the cancer-free participants at Visit 5 first and then go back to choose the same group of participants visit 2 because this can make sure participants in both training set and validation set are cancer-free. The remaining cohort will be used in specific aim 2.

**Stage A.** Using the training set, we will calculate the mean difference in levels of each protein between Visit 2 and Visit 5 (~ 20 years apart) and the standard deviation for each protein level at visit 2. Then, we will create a standardized ratio for each protein value by dividing the mean difference by its standard deviation. Finally, we will rank the proteins based on their standardized values. The top 1250 proteins (around 25% of the ~5000 proteins) with the largest intra-individual changes in blood levels over time will be included in **Panel 1**.

Of note, if we will also be able to look at proteins that have largest inter-individual change over time, we might include the top 1250 proteins with largest inter-individual change to Panel 1 if these proteins are not found to be with largest intra-individual changes.

**Stage B.** In the training set, proteins from this panel will be used to fit a regression model to predict proteomic aging clock using multiple linear regression (MLR), Klemra and Doubal method (K+D method),<sup>31</sup> or other penalized regressions, e.g., elastic net.<sup>22</sup> Of note, one regression will be used for all proteins. When fitting the regression in cancer-free people, we will assume chronological age is a surrogate marker of the proteomic aging clock. We will use the regression co-efficient for each protein as its weight to build the formula to predict proteomic aging clock.

For instance, if we use **MLR** to fit the regression, the formula will be:

$$\text{Proteomic aging clock} = \beta_0 + \sum_{j=1}^{1250} \beta_j \text{Protein}_{i,j} + \beta_{1251} \text{Sex} + \beta_{1252} \text{Racecenter} + \beta_{1253} \text{BMI} + \beta_{1254} \text{Smoking status}$$

Here, proteomic aging clock is the estimate of proteomic age. Protein<sub>j</sub> is the level of j<sup>th</sup> protein from the panel. **Panel 1** includes the top 1250 proteins with the largest intra-individual changes in blood levels, therefore, 1250 proteins will be included in this MLR.

If we use **K+D method**,<sup>31</sup>

$$Proteomic\ aging\ clock = \frac{\sum_{j=1}^m (Protein_{ij} - q_j) \frac{k_{ij}}{s_{ij}^2} + \frac{C}{S_{Proteomic\ aging\ clock}^2}}{\sum_{j=1}^m \left(\frac{k_{ij}}{s_{ij}}\right)^2 + \frac{1}{S_B^2}}$$

The parameters in the equation will be calculated following the instructions in Klemra and Doubal 2006.<sup>31</sup>

If we use **elastic net**, the formula will be:

$$Proteomic\ aging\ clock = \beta_0 + \sum_{j=1}^m \beta_j Protein_j + \beta_{m+1} Sex + \beta_{m+2} Racecenter + \beta_{m+3} BMI + \beta_{m+4} Smoking\ status$$

Compared to the MLR model, the “m” proteins will be selected using the elastic net, which penalizes the coefficients using L<sub>1</sub> and L<sub>2</sub> norms.

**Stage C.** In the validation set, we will predict proteomic aging clock for the same set of individuals at visit 5, multiplying their protein levels at visit 5 and the coefficients estimated in the training set.

We will estimate the prediction accuracy of each proteomic aging clock using Pearson and Spearman correlations (between proteomic aging clock and chronological age) as well as by calculating the absolute delta age (difference between the proteomic aging clock and chronological age) in the validation set. A proteomic age estimator will be considered useful if its correlation with chronological age exceeds 0.8 in the validation set.<sup>32</sup>

**Panel 2:** We will develop this panel by looking at associations between chronological age and protein levels among ARIC cancer-free participants.

**Stage A.** We will determine proteins associated with age using a cross-sectional analysis in one half of ARIC cancer-free participants as discussed in Tanaka 2018.<sup>22</sup> In the training set, we will apply linear regression for each protein separately to assess the association of chronological age at Visit 2, after adjustment for sex, race-center, and the most important factors in aging, i.e., BMI and smoking status (see equation below). A false discovery rate (FDR) corrected threshold of P < 0.05 will be considered significant. The significant proteins based on FDR p-value will be included in this panel.

Equation for the linear regression:

$$Protein_i\ Level = \beta_0 + \beta_1 Chronological\ age + \beta_2 Sex + \beta_3 Racecenter + \beta_4 BMI + \beta_5 Smoking\ status$$

Here, protein<sub>i</sub> represents the i<sup>th</sup> protein in the ~5000 proteins.

Stage B. The clock will be created as described in approach 1.

Stage C. The clock will be validated as described in approach 1

Of note, Proteins in Panels 1 and 2 may overlap a lot (both capturing aspects of chronological age, but Panel 1 should also capture proteins that change in a more extreme way that just age alone).

**Panel 3 and Panel 4:** we will use two panels that were shown to be associated with aging in previous systematic review and validating in our population.

Stage A. We will use each panel of proteins proposed in the latest systematic review of proteomic-based aging research.<sup>8</sup> In the systematic review, Johnson et al. proposed two versions of proteomic aging clock: the 23-protein panel (**Panel 3**) and the 83-protein panel (**Panel 4**). The 23-protein panel and 83-protein panel included plasma proteins that were reported to be significantly associated with chronological age in 4+ and 3+ different studies, respectively. They evaluated the prediction accuracy of the two panels using Pearson and Spearman correlations between proteomic aging clock and chronological age, as well as by calculating the mean absolute delta age in the INTERVAL cohort, which comprised of 3,301 healthy individuals aged 18-76 years with a median age of 45 (Q1 = 31, Q3 = 55).<sup>33</sup> They measured the proteins in those two panels using the SomaScan assay. In their validation set (1123 participants from the INTERVAL cohort), the 23-protein and 83-protein panel had a Pearson correlation of 0.66 and 0.87 with chronological age, respectively, Spearman correlation of 0.69 and 0.88, respectively, and mean absolute delta age of 8.17 and 4.88 in year respectively.<sup>8</sup>

Stage B. The clock will be created as described in approach 1.

Stage C. The clock will be validated as described in approach 1.

To examine association with cancer, we may choose the most robust proteomic aging clock based on the correlations and absolute delta age or apply two best proteomic aging clocks in the analysis of cancer risk. We will work with a statistician to decide on the best way for creating the clock.

Since this area of research is novel and developing, we may also include senescence biomarkers (if they present in ARIC) that have been established as aging biomarkers in the individual studies of cancer, such as breast cancer,<sup>34</sup> that have been already conducted or will be conducted during working on the proposed analysis.

Of note, a total of 32 research publications were included the latest systematic review. All the 32 studies measured fewer proteins (< 5000) compared to SomaScan in ARIC. Therefore, we expect that Panels 3 and 4 may not provide more robust results than Panels 1 and 2. We may include established senescence biomarkers associated with aging (if they present in ARIC) to Panels 3 and 4 to determine if these existing panels can be improved.



**Specific Aim 2.** Determine the association between the pre-diagnostic proteomic age acceleration and the risk of overall cancer and specific cancer types.

In this analysis, we will include the remaining participants at Visit 2 that are not selected in Aim 1.

Proteomic age acceleration will be calculated by regressing each participant’s proteomic aging clock on their chronological age and using the corresponding residual value in the linear regression models. A positive value of age acceleration indicates that the proteomic age is higher than the chronological age.<sup>35</sup>

Cox proportional hazards regression will be used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer risk associated with proteomic age acceleration. The proportional hazards assumption will be tested by including an interaction term between proteomic age acceleration and follow-up time in the Cox model. Person-years will be estimated from the start of follow-up at Visit 2 until the date of cancer diagnosis, censor at loss of follow-up or death, or the end of follow-up, whichever occurred first. The proteomic age acceleration will be examined as a continuous variable, but will be transformed or categorized into quartiles if a nonlinear relationship with cancer risk is observed. To account for the change of proteomic age acceleration during follow-up, we will model proteomic age acceleration as a time-dependent variable, which is defined as a variable whose value for a given subject may change over time. We will adjust for age, sex, race-center, eGFR, and liver function in the analysis. We will also adjust for BMI, smoking status, pack-years of smoking, diabetes, use of NSAIDs, and hormone therapy, to determine whether the accelerated aging clocks are simply capturing cancer risk factors. We may also adjust socioeconomic status (SES), because those of lower SES may have less access to care/less access to medications to treat/cure diseases, so the aging clocks that may end up differing.

**Power calculations**

**Specific Aim 1.** The sample size that is needed for validating an age estimator depends on the accuracy of the age estimator. Based on Horvath et al.,<sup>32</sup> 62 test samples would need if a true correlation is 0.9. A sample of 205, 404, and 867 would need to test a true correlation of 0.80, 0.70, and 0.50, respectively. We expect to have 2896 cancer-free participants from Visit 2 used as the training set and 2896 cancer-free participants from Visit 5 used as the validation set.

**Specific Aim 2.** The power calculations with cancer incidence up to 2015 are presented in Table 1 for **Specific Aim 2**. Categorizing into groups is a conservative approach to estimate power for a continuous variable. Thus, in *Specific Aims 1 and 2*, we will estimate power for the two situations below: a) dichotomize proteomic aging clock at median (higher and lower groups), and b) categorize proteomic aging clock at quartiles (Q1, Q2, Q3, and Q4) based on its distribution at V2.

<b>Table 1.</b> Power calculation in ARIC participants (80% power, alpha = 0.05, two-sided) for the association between pre-diagnosis proteomic age acceleration and overall cancer risk, most common individual cancer risk, obesity-related cancer risk, and smoking-related cancer risk				
Cancer type	Number of cancer cases	Number of all participants <sup>a</sup>	Minimal detectable risk for dichotomized exposure	Minimal detectable risk for quartiles

Any cancer	4,407	9,693	1.13	1.18
Breast cancer	621	9,693	1.37	1.57
Ovarian cancer	68	9,693	2.62	3.89
Endometrial cancer	115	9,693	2.09	2.83
Kidney cancer	145	9,693	1.93	2.53
CRC	411	9,693	1.48	1.74
Pancreatic cancer	136	9,693	1.97	2.62
Lung cancer	680	9,693	1.35	1.54
Obesity-related cancer <sup>b</sup>	1,605	9,693	1.22	1.32
Smoking-related cancer <sup>c</sup>	1,328	9,693	1.24	1.36

<sup>a</sup>The number of all participants at Visit 2 is 9,693 because we use 2896 cancer-free participants to develop the clock.  
<sup>b</sup>The number of obesity-related cancer is calculated by combining the number breast (n = 621), colorectal (n = 411), endometrial (n = 115), ovarian (n = 68), kidney (n = 145), pancreatic (n = 136) cancers, liver cancer (n = 36), and lethal prostate cancer (approximately 100 cases).  
<sup>c</sup>The number of smoking-related cancer is calculated by combining the number lung (n = 680), pancreatic (n = 136), esophageal (approximately 35 cases), bladder (n = 204), stomach (n = 67), liver (n = 36), cervix (n = 25), and kidney cancers.

**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.csc.c.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)?**

MP3515 A comparison of the inflammatory proteome in cancer survivors and individuals with no cancer history.

MP3482 Plasma Proteins and All-Cause Mortality in Cancer Survivors in ARIC (MP3515 is a subset of MP3482 for a doctoral dissertation)

MP3057 Repeatability and Longitudinal Variability of the Plasma Proteome.  
MP3617 Association between functional MICA polymorphisms, soluble MICA levels, colorectal cancer incidence and mortality: Results from the Atherosclerosis Risk in Communities study.

**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\* \_**

AS1995.04 Cancer Study

AS2011.07 Enhancing ARIC Infrastructure to Yield a New Cancer Epidemiology Cohort

AS2017.27 Proteomic longitudinal ARIC study: SOMAscan of multiple visits

AS2019.15 MHC class I chain-related proteins, functional polymorphism and colorectal cancer

AS2020.32 Proteomic Aging Clock and Colorectal Cancer

**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.csc.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.csc.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.

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