

**ARIC Manuscript Proposal #3563**

**PC Reviewed:** 2/11/20  
**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:** The Performance of Cardiovascular Risk Scores in Cancer Survivors

**b. Abbreviated Title (Length 26 characters):** CVD risk in Cancer Survivors

**2. Writing Group:**

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Kenneth Butler, and Kunihiro Matsashita)

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

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### 3. Timeline:

We expect to submit this manuscript for publication within one year of approval.

### 4. Rationale:

Cancer is a common diagnosis in the United States, with a lifetime risk of 30% for women and 50% for men.<sup>1</sup> Since 1975, cancer incidence has increased, from 400 to 432 cases per 100,000 population. At the same time, five-year survival has risen from 49% to 70%, due to advances in early detection and treatment.<sup>2</sup> This has resulted in a growing population of cancer survivors—currently nearly 17 million people. As of 2019, cancer survivors made up 5% of all Americans and over 22% of adults over 65 years of age.<sup>3,4</sup> Growing evidence suggests that cancer survivors are at elevated risk for cardiovascular disease (CVD).<sup>5</sup> CVD risk prediction tools such as the Framingham Risk Score (FRS) and Pooled Cohort Equations (PCE) are urgently needed for oncologists and other physicians to determine treatment for their patients.<sup>6</sup> However, there is concern that commonly used scores underestimate CVD risk in cancer survivors.<sup>6</sup>

The FRS and PCE are standard tools used in clinical care of middle-aged and older adults. The FRS, derived in 2008, evaluates risk for overall CVD, including coronary heart disease (CHD), cerebrovascular disease, peripheral vascular disease, and heart failure,<sup>7</sup> while the PCE were developed in 2013 to evaluate risk of Atherosclerotic Cardiovascular Disease Events (ASCVD), which include non-fatal myocardial infarction, CHD death, and stroke, but not heart failure or peripheral artery disease. The PCE were designed in part to extend the generalizability of the Framingham score to a more racially diverse (Black and White) population. However, the PCE overestimated or underestimated risk in several validation studies.<sup>8-10</sup> The American College of Cardiologists and American Heart Association recommend the PCE for clinical prediction, but acknowledge the value of other scores, including the FRS for estimating CVD risk in clinical practice.<sup>11,12</sup> Both scores include similar components; CVD risk factors such as age, sex, race, cholesterol, systolic blood pressure, diabetes, and smoking status, although they use different equations to derive estimates of ten-year CVD risk.

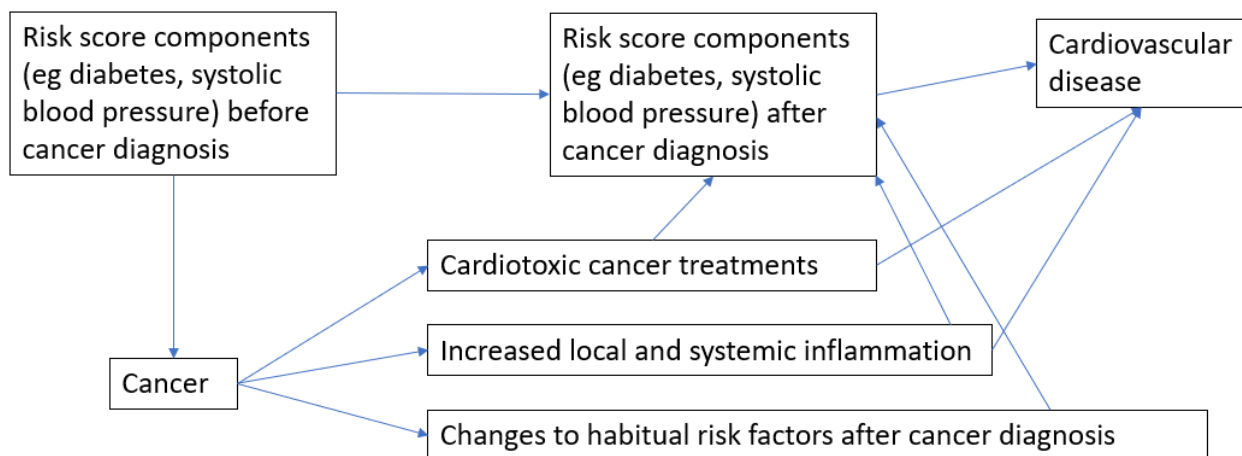
Studies during last decade have reported that risk of CVD is increased among cancer survivors.<sup>5,13,14</sup> For instance, in a claims-based analysis of 36,232 cancer survivors and 73,545 cancer-free controls the CVD risk was elevated in survivors of breast cancer (IRR: 1.13, 95% CI: 1.06-1.22) and lung/ bronchus cancer (IRR: 1.58, 95% CI: 1.30-1.90), multiple myeloma (IRR: 1.70, 95% CI: 1.31-2.21), non-Hodgkin's lymphoma (IRR: 1.41, 95% CI: 1.06-1.88), and ovarian cancer (IRR: 1.41, 95% CI: 1.06-1.88), although the CVD risk was not increased in survivors of all cancers (Incidence Rate Ratio (IRR): 1.02, 95% CI 0.99-1.06).<sup>5</sup> In a prospective cohort of 2512 testicular cancer survivors, standardized incidence rates (SIR) of CVD were 17% higher than population estimates (SIR: 1.17, 95% CI: 1.04-1.31).<sup>13</sup> In a population-based cohort study of participants with and without breast cancer patients matched by age, the hazard ratio of CVD death was 1.8 (95% CI: 1.5-2.1) for those with breast cancer compared to age-matched breast cancer-free controls.<sup>14</sup>

There are several plausible mechanisms that may account for increased CVD risk in cancer patients. CVD and cancer share several common risk factors, including age, sex, obesity, smoking, alcohol consumption and diabetes, and biological mechanisms such as inflammation and oxidative stress play a role in both diseases.<sup>15</sup> If shared causal factors explain most of the

increased CVD risk observed in cancer survivors, the FRS and PCE may predict CVD risk as well in cancer survivors as in the general population.

However, there are additional factors that could modify CVD risk in cancer survivors. Several cancer treatments are cardiotoxic, including chest radiation for lung/bronchus cancer and left-side breast,<sup>16,17</sup> chemotherapeutic agents, especially anthracyclines,<sup>18-20</sup> and hormone and immunotherapies.<sup>21-23</sup> Also, having cancer itself is linked to increased local and systemic inflammation<sup>24</sup> which can contribute to increased CVD risk.<sup>25</sup> In addition, cancer diagnosis and treatment may lead to behavioral changes, such as smoking cessation,<sup>26</sup> resulting in misclassification in subsequent risk scores. A directed acyclic graph depicting the causal relationships between risk scores, cancer status, and CVD risk is shown in Figure 1. In summary, additional CVD risk associated with cancer and treatments may not be reflected in the PCE or Framingham scores.

**Figure 1: Causal Diagram of the Associations between CVD Risk Scores, Cancer Status, and CVD events**



Previous studies in childhood cancer survivors have established the inadequacy of commonly used risk scores in that group, and a CVD risk score specifically developed for childhood cancer survivors is now in use.<sup>6,27</sup> A small study have found that the FRS underestimates CVD risk in adult survivors of breast cancer<sup>28</sup>. However, to our knowledge, the accuracy of the FRS and PCE have not been comprehensively estimated in middle-aged or older survivors of adult cancer.

It is important to examine whether risk prediction tools, such as the FRS and PCE, perform effectively in cancer patients because they are used by physicians to estimate their patients' CVD risk and prescribe statins.<sup>29</sup> Based on those recommendations, high-risk patients can modify their diet and lifestyle behaviors (e.g. smoking, diet, and physical activity) to reduce their risk of cardiac events. If these tools underestimate risk for cancer survivors, patients may not receive needed treatments and recommendations, resulting in greater morbidity and mortality.

The ARIC study is a unique setting to investigate whether the FRS and PCE scores accurately predict CVD risk in cancer survivors: it has 14,688 participants, including over 1200 cancer survivors in this analysis, over 30 years of follow-up for CVD and detailed information on CVD risk factors at each visit.

## 5. Main Hypothesis/Study Questions:

**Hypothesis:** The FRS and PCE scores will underestimate CVD risk among cancer survivors, and the association between CVD risk scores and CVD events will be weaker among survivors than participants without cancer.

**Aim 1:** To evaluate the performance of two risk scores (the FRS and PCE scores) in cancer survivors and compare the calibration and discrimination of each score in participants with and without cancer

**Aim 2:** To estimate the difference between the longitudinal association each CVD risk score with CVD risk in participants with and without cancer

## 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).

We will appraise the performance of the FRS and PCE scores in cancer survivors and compare their calibration and discrimination in cancer survivors to matched controls who are cancer-free at the start of follow-up. Scores will be calculated in cancer survivors at the first visit least one year after cancer diagnosis.

Each cancer survivor will be matched by index date, age, sex, race, and study center with up to 5 randomly selected controls who are CVD-free and cancer-free at the start of follow-up (the first visit at least one year after index date). The index date for each cancer-free participant will be equal to the date of cancer diagnosis for the matched cancer survivor. Incidence density sampling will be used to select controls. Participants who later develop cancer will be eligible for selection as controls for participants with earlier cancer diagnoses.

### Participants: Inclusions and Exclusions

Cancer survivors will be included if they have a confirmed diagnosis of any primary cancer. Incident cancer cases were ascertained via linkage to state cancer registries, hospital discharge summaries, and medical record abstraction.<sup>30</sup> Participants will be excluded if they have not consented to participate in non-CVD studies, belong to races other than white or black, or have prevalent cancer at Visit 1 or CVD before the start of follow-up.

Our primary analysis will include survivors of all primary invasive cancers other than non-melanoma skin cancer. In addition, we hope to examine each of our aims in survivors of breast, lung/bronchus, colorectal, prostate, and hematopoietic cancers but believe there will be too few CVD events for these analyses, in which case we may later evaluate this in conjunction with a larger cohort.

### Calculation of the FRS and PCE

The FRS and PCE will be calculated for each participant with cancer and matched participants at least one year after cancer diagnosis or index date. Measuring risk scores at least one year after cancer diagnosis ensures that risk scores are minimally impacted by the biological and psychosocial changes associated with ongoing cancer diagnosis and treatment.<sup>31</sup> Each component in the FRS and PCE was measured at each ARIC study visit, so scores will be calculated using measures from the first study visit that occurred at least one year after the index

date If the cancer diagnosis occurred less than one year before the visit, the scores will be calculated at the following visit (Table 1).

**Table 1: Study Design and Estimated Sample Size and Event Count**

Start of follow-up/ calculation of risk scores	First date of cancer diagnosis corresponding to the risk score in column 1	Last date of cancer diagnosis corresponding to the risk score in column 1	Number of Cancer Survivors/ Matched controls*	CVD Events (Aim 1) for Cancer Survivors/ Matched controls*	CVD Events (Aim 2) for Cancer Survivors/ Matched controls**
Visit 2: 1990-1992	After Visit 1	One year before Visit 2	119/595	14/70	30/150
Visit 3: 1993-1995	Less than one year before Visit 2	One year before Visit 3	175/875	18/90	40/200
Visit 4: 1996-1998	Less than one year before Visit 3	One year before Visit 4	205/1025	24/120	52/260
Visit 5: 2011-2013	Less than one year before Visit 4	One year before Visit 5	646/3230	72/360	72/360
Visit 6: 2016-2017	Less than one year before Visit 5	One year before Visit 6	112/560	4/20	4/20
Visit 7: 2018-2019	Less than one year before Visit 6	One year before Visit 7	2/10	0	0
<b>Total</b>			<b>1259/6295</b>	<b>132/660</b>	<b>198/990</b>

\* Estimated for cancer survivors and up to 5 participants without cancer per cancer survivor, matched by index date; including up to ten years of follow-up

\*\*Estimated for cancer survivors and 5 participants without cancer per cancer survivor, matched by index date; including all available follow-up

Note: CVD events shown are conservative estimates because they do not include all endpoints (e.g. peripheral artery disease) and do not account for censoring.

The FRS is calculated using different scores for men and women, while the PCE include four scores for Black and White men, and Black and White women. The FRS and PCE include the same components: age, total cholesterol, HDL cholesterol, systolic blood pressure (with and without treatment), diabetes status, and current smoking status; but with different subgroups and different coefficients for the components (Table 2).

To create each score, we will multiply the value for each component for each ARIC participant by a coefficient derived from literature and sum them. Diabetes and smoking status will be dichotomous and continuous values for age, total cholesterol, HDL cholesterol, and systolic blood pressure will be log-transformed for each score. All scores used in our analysis are shown in Table 2.

For PCE scores, a baseline ten-year survival rate for each score in each group is then raised to the power of the summed score to estimate ten-year CVD survival. For the FRS, the baseline ten-year survival rate is raised to the sum score minus the average summed score. For both scores, ten-year survival is subtracted from one to estimate ten-year CVD risk (Table 2).<sup>32,33</sup>

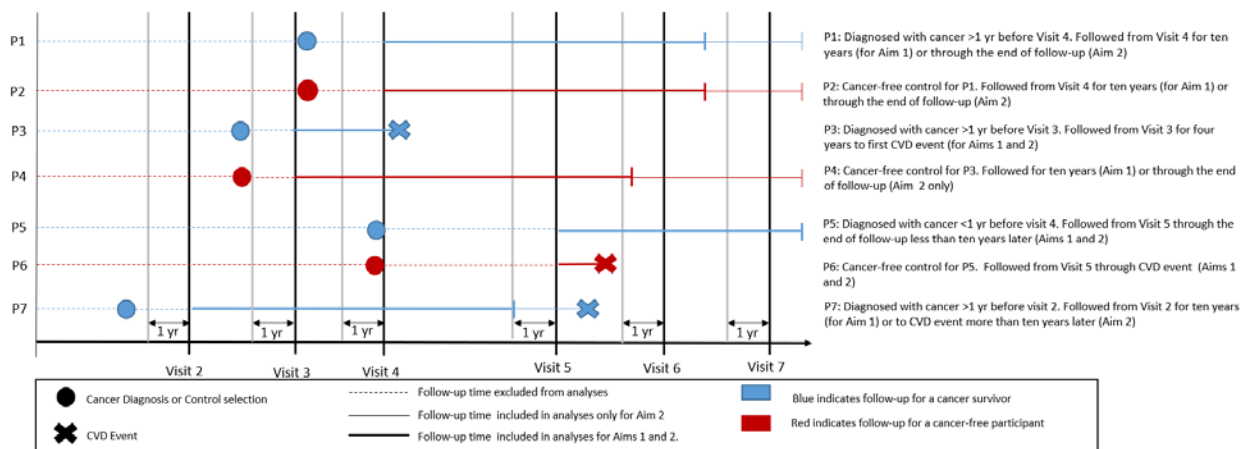
**Table 2:** Equations Used to Calculate 10-year CVD Risk in Each Subgroup for the Framingham Risk Score and Pooled Cohort Equations

	Calculation of Risk Score	Calculation of 10-year risk
<b>Framingham Risk Score</b>		
Men	$S = \ln(\text{age}) * 3.06 + \ln(\text{total cholesterol}) * 1.12 + \ln(\text{HDL cholesterol}) * -0.93 + \ln(\text{untreated systolic blood pressure}) * 1.93 + \ln(\text{treated systolic blood pressure}) * 2.82 + \text{current smoker} * 0.53 + \text{diabetes} * 0.69$	$1 - 0.88036^{S-5}$
Women	$S = \ln(\text{age}) * 2.33 + \ln(\text{total cholesterol}) * 1.21 + \ln(\text{HDL cholesterol}) * -0.71 + \ln(\text{untreated systolic blood pressure}) * 2.76 + \ln(\text{treated systolic blood pressure}) * 2.83 + \text{current smoker} * 0.53 + \text{diabetes} * 0.69$	$1 - 0.95012^{S-5}$
<b>Pooled Cohort Equations</b>		
Black Men	$S = \ln(\text{age}) * 2.47 + \ln(\text{total cholesterol}) * 0.30 + \ln(\text{HDL cholesterol}) * -0.31 + \ln(\text{treated systolic blood pressure}) * 1.916 + \ln(\text{untreated systolic blood pressure}) * 1.81 + \text{current smoker} * 0.55 + \text{diabetes} * 0.65$	$1 - 0.8954^S$
White Men	$S = \ln(\text{age}) * 12.34 + \ln(\text{total cholesterol}) * 11.85 + \ln(\text{age}) * \ln(\text{total cholesterol}) * -2.66 + \ln(\text{HDL cholesterol}) * -7.99 + \ln(\text{age}) * \ln(\text{HDL cholesterol}) * 1.77 + \ln(\text{treated systolic blood pressure}) * 1.80 + \ln(\text{untreated systolic blood pressure}) * 1.76 + \text{current smoker} * 7.83 + \ln(\text{age}) * \text{current smoker} * -1.80 + \text{diabetes} * 0.66$	$1 - 0.9144^S$
Black Women	$S = \ln(\text{age}) * 17.11 + \ln(\text{total cholesterol}) * 0.94 + \ln(\text{HDL cholesterol}) * -18.92 + \ln(\text{age}) * \ln(\text{HDL cholesterol}) * 4.48 + \ln(\text{treated systolic blood pressure}) * 29.29 + \ln(\text{age}) * \ln(\text{treated systolic blood pressure}) * 6.43 + \ln(\text{untreated systolic blood Pressure}) * 27.82 + \ln(\text{age}) * \ln(\text{untreated systolic blood pressure}) * -6.09 + \text{current smoker} * 0.69 + \text{diabetes} * 0.87$	$1 - 0.9533^S$
White Women	$S = \ln(\text{age}) * -29.80 + \ln(\text{age}) * \ln(\text{age}) * 4.88 + \ln(\text{total cholesterol}) * 13.54 + \ln(\text{age}) * \ln(\text{total cholesterol}) * -3.11 + \ln(\text{HDL cholesterol}) * -13.58 + \ln(\text{age}) * \ln(\text{HDL cholesterol}) * 3.15 + \ln(\text{treated systolic blood pressure}) * 2.02 + \ln(\text{untreated systolic blood pressure}) * 1.96 + \text{current smoker} * 7.57 + \ln(\text{age}) * \text{current smoker} * -1.67 + \text{diabetes} * 0.66$	$1 - 0.9665^S$

## Follow-up

The start of follow-up for each participant will be the date of the visit where the risk scores are calculated. Because the Framingham and PCE Scores evaluate ten-year risk of CVD, for Aim 1, participants with cancer will be followed for ten years, to the first CVD event, the end of follow-up, death or loss to follow-up, whichever occurs first. In order to account for censoring, we will use Kaplan-Meier tables to estimate the actual number of CVD events over ten years (see Statistical Analysis below). For Aim 2, the follow up will end at the first CVD event, the end of follow-up, death or loss to follow-up, whichever occurs first. Follow-up for a series of hypothetical participants is summarized in Figure 2.

**Figure 2: Visualization of Study Follow-up for a Series of Hypothetical participants**



## Outcomes: CHD risk for FRS and ASCVD risk for PCE

The FRS and PCE Scores evaluate different CVD outcomes. The FRS estimates risk of the first event of several CVD outcomes, including coronary heart disease (including coronary death, myocardial infarction (MI), coronary insufficiency, and angina), cerebrovascular disease (ischemic or hemorrhagic stroke or transient ischemic attack (TIA)), peripheral artery disease, or heart failure. The PCE Scores estimate risk for Atherosclerotic Cardiovascular Disease Events (ASCVD), which include nonfatal MI, coronary heart disease death, and ischemic stroke, but not peripheral artery disease. In ARIC, all CVD outcomes are ascertained through hospital discharge records, and review of death records. For our analysis, the individual components of each CVD outcome will be defined as follows:

*Coronary heart disease:* Definite or probable MI, definite fatal CHD, or coronary revascularization.

*Cerebrovascular Disease:* Definite or probable ischemic or hemorrhagic stroke

*Heart Failure:* Hospitalization or death from heart failure

*Peripheral Artery Disease:* Hospitalization for peripheral artery disease (ICD-9 codes 440.XX, 38.18, 39.25, 39.29, 39.50)<sup>34</sup>

## **Covariates**

Where possible, shared cancer and CVD risk factors (for instance, body mass index) will be assessed at the same study visit at which the scores (FRS and PCE) are calculated. For risk factors such as alcohol consumption and physical activity that were not collected at all visits, the most recent measurement before cancer diagnosis will be used.

## **Statistical Analysis**

**Aim 1:** To estimate the calibration of the PCE and FRS, predicted and estimated “actual” CVD rates will be compared in cancer survivors and participants without cancer. Participants will be divided into deciles of 10-year predicted CVD risk based on their Framingham or PCE risk scores. Because loss to follow-up and follow-up of less than ten years after the index date for many participants will prevent us from observing all CVD events that occur in the ten years following score calculation, we will use Kaplan-Meier tables to estimate the number of actual events occurring in ten years. To calculate the estimated number of events, the Kaplan-Meier event rate will be multiplied by the number of participants in each decile. This method was applied to the evaluation of CVD risk score performance in a paper by J. Wolfson who also serves as a co-author on this proposal.<sup>35</sup> Agreement between predicted and Kaplan-Meier-estimated events will be evaluated using a Hosmer-Lemeshow goodness-of-fit test. To estimate discrimination, we will calculate Harrell’s C statistic. For each model, a C-statistic greater than or equal to 0.7 will indicate adequate discrimination.<sup>36,37</sup> Calibration and discrimination will be evaluated separately for each risk score in cancer survivors and matched controls. Because such a large proportion of older adults are cancer survivors, any under- or overestimation in cancer survivors compared to matched controls will be considered clinically meaningful.

**Aim 2:** To evaluate whether each risk score is more weakly associated with CVD risk in cancer survivors than in cancer-free participants, we will use conditional Poisson regression. Participants will be divided by into high ( $\geq 7.5\%$ ) medium (5% to  $< 7.5\%$ ) and low ( $< 5\%$ ) risk categories based on PCE and FRS estimated CVD risk. If there is sufficient sample size, we will divide the highest category into intermediate risk (7.5 to  $< 20\%$ ) and high risk ( $\geq 20\%$ ) groups, in accordance with current American Heart Association/ American College of Cardiology recommendations.<sup>32</sup> Conditional Poisson regression models will be fit to estimate the estimate the association of predicted risk with CVD incidence (defined as CVD events for the FRS and ASCVD events for the PCE Scores) while accounting for matching. Additional independent variables will be cancer survivor status and a term for interaction between cancer status and the risk score. If the *p*-value for the interaction term is less than 0.05, stratified analyses will be conducted in participants with and without cancer. For both the FRS and PCE, these models will be used to calculate the incidence rate in each category of CVD risk among cancer survivors and matched cancer-free participants. The relative excess risk due to interaction (RERI) will also be calculated.<sup>38</sup>

## **Power and Sample Size**

We expect to see at least 132 CVD events among cancer survivors and over 650 among controls. Assuming  $\alpha=0.05$ , an overall incidence rate ratio of 3.88 for the highest risk category ( $\geq 7.5\%$ ) versus the lowest ( $< 5\%$ ), we expect to have 80% power to detect a difference in incidence rate ratios of 0.6 between participants with and without cancer. According to a recent



study by Collins et al (2016) , a minimum of 100 events in a sample of at least 200 participants are adequate to evaluate the performance of multivariable risk scores.<sup>39</sup> We expect that our sample size will be adequate to estimate calibration and discrimination in all cancer survivors and their matched controls. Currently, we are exploring options to combine ARIC data with the data from other studies to increase our sample size in order to evaluate calibration and discrimination for the survivors of individual cancers.

### **Sensitivity Analyses**

We will conduct several sensitivity analyses:

- Repeat all analyses using modified five-year risk scores, in order to account for the short follow-up following visits 5 and 6.
- Repeat all analyses with visit 5 as a baseline, with modified five-year risk scores
- Repeat our analyses including only five-year cancer survivors (and cancer-free participants in Aim 2), beginning follow-up at the visit that was closest to but at least five years after cancer diagnosis (or index date).
- Repeat all analyses after excluding those who had more than three years between cancer diagnosis and the visit at which scores were calculated in order to account for any differences between participants with a long period of follow-up between diagnosis and score calculation, compared to those with a study visit shortly after cancer diagnosis.

### **Additional Analyses**

We will conduct three additional analyses:

- We are interested in the performance of scores calculated before cancer diagnosis and will examine all aims using components measured at the most recent visit before cancer diagnosis or index date.
- We will repeat our analysis in survivors of any site-specific cancers that have sufficient CVD events for analysis.
- We will evaluate the performance of the FRS and PCE in the ARIC cohort overall.

### **Limitations**

The primary limitations of this study include a lack of information on cardiotoxic cancer treatments and low power to evaluate ten-year CVD incidence among survivors of specific cancers.

In addition, over sixty percent of participants will begin follow-up at visit 5 or 6, less than ten years before endpoint surveillance is complete. We will use Kaplan-Meier estimation to adjust for censoring.

Finally, because of the long gap between study visits 4 and 5, the actual time from cancer diagnosis to the collection of risk score measures and the start of follow-up will vary. To account for this, we will (1) adjust for this time window in our analysis in Aims 1 and 2 and (2) in sensitivity analyses, exclude participants with long periods between cancer diagnoses and risk score calculation.

**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 \_X\_ 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.unc.edu/aric/mantrack/maintain/search/dtSearch.html>**

\_\_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)?**

- 2912: Florido et al. Subclinical Myocardial Damage among Cancer Survivors in ARIC
- 3028: Florido et al. Cardiovascular Risk among Cancer Survivors in the ARIC study  
**Note:** Dr. Florido has reviewed our manuscript proposal and has not raised any concerns about similarities between our manuscript and #3028.
- 3257: Moran et al. Heart Failure Prediction in Cancer Survivors **Note:** This proposal focuses on heart failure prediction using biomarkers.

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

**11.b. If yes, is the proposal**

\_\_X\_\_ **A. primarily the result of an ancillary study (list number\* \_\_\_11B\_\_\_)**

\_\_\_ **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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