ARIC Manuscript Proposal Form

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Publication Committee Review Date: **_02/11/25**
ARIC Manuscript Proposal Number: **# 4605**

1.a. Full Title: Large-Scale Proteomic Profiling of Incident Heart Failure and Its Subtypes in Older Adults

b. Abbreviated Title (Length 26 characters): Proteomics of HF in Elders

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __JNN___ **[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 (The ARIC author should be involved enough in ARIC to

be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline: A manuscript was completed and submitted to Circulation Genomic and Precision Medicine, receiving a decision of "revise". A principal critique was lack of replication of aptamer hits identified in relation to incident heart failure (HF) or its subtypes in a meta-analysis of the Cardiovascular Health Study (CHS) and Aging, Genes and Environment Study – Reykjavik Study (AGES-RS). We are seeking to replicate these aptamers in ARIC and revise the manuscript ahead of the resubmission deadline of April 7, 2025.

4. Rationale: Heart failure and its two major subtypes, HF with preserved (HFpEF) or reduced (HFrEF) ejection fraction, impose high morbidity and mortality in elders.[1] HFpEF and HFrEF have different and heterogenous pathophysiologic underpinnings, and respond differently to therapies.[2-4] Important strides have been made in HF treatment.[5] But therapeutic options remain limited, particularly for HFpEF, and prognosis remains poor.[6,7] Improved preventive and therapeutic approaches require better understanding of the molecular determinants of these disorders.

Advances in proteomics have permitted high-throughput measurement of thousands of proteins in biofluids.[8] As the major effectors of gene function, and reflecting the input of environmental influences, proteins are key candidates for unraveling the molecular basis of human diseases.[9] What is more, a majority of approved drugs act upon proteins, attesting to the potential to target proteins to modify disease processes.[10] Use of Mendelian randomization analysis, predicated on certain assumptions, allows causal inferences, which can dramatically increase the likelihood that targeting identified proteins will yield therapeutic benefit.[11,12]

Recent proteomic investigations, including studies in ARIC, discovered several proteins to be associated with incident HF,[13-18] with associations extended to HF subtypes.[17,18] Existing proteomic studies have been limited, however, in their capacity to evaluate HF subtypes separately as a result of modest event numbers. Nor have such studies been in a position to pursue causal inference specifically for HF subtypes through Mendelian randomization (MR) approaches.

We undertook large-scale plasma proteomics in CHS, a U.S. population-based cohort study of older adults using SomaLogic's high-throughput aptamer technology, and meta-analyzed our findings with those of AGES-RS, a European population-based cohort study of elders that applied a similar proteomic platform, in order to identify protein markers associated

with overall HF, as well as HFpEF and HFrEF. We then leveraged a recently completed GWAS of HF and its subtypes, the HERMES2 consortium,[19] to investigate the potential causal basis of identified protein associations. Our analyses identified 128 aptamers (119 unique proteins) associated with overall HF, 15 aptamers (15 proteins) associated with HFpEF, and 12 aptamers (11 proteins) associated with HFrEF. Seven of these proteins had suggestive evidence of causality in their associations with HF in MR analysis, two of them also with HFpEF, while another two had suggestive evidence of causality with HFrEF. Of new protein associations in CHS and AGES-RS, 68 are new in relation to HF, 1 in relation to HFpEF and 1 in relation to HFrEF.

Here we propose to replicate the 128 aptamer associations with HF, the 15 aptamer associations with HFpEF and the 12 aptamer associations with HFrEF identified in the meta-analysis of CHS (17.8% Black) and AGES-RS (100% European) in the biracial ARIC cohort.

5. Main Hypothesis/Study Aims: We sought to test the hypothesis that, using the SomaLogic 5K platform, new proteins could be identified as prospectively associated with onset of HF, HFpEF and HFrEF in two population-based cohort studies of elders, and that some of these would be supported as potentially causal in MR analysis. Here we seek to test the hypothesis that our aptamer hits in CHS and AGES-RS will replicate in ARIC.

6. Design and analysis - please address the following aspects:

a) inclusion/exclusion

The study sample for replication of the CHS and AGES-RS findings will be ARIC participants free of prevalent HF with available SomaLogic 5K proteomic measures at Visit (V) 5.

b) study design

Prospective cohort study analyzing the relationship of identified aptamer hits from CHS and AGES-RS with incidence of overall HF (n=128 aptamers), HFpEF (n=15 aptamers) or HFrEF (n=12 aptamers).

c) outcome and other variables of interest with specific reference to the time of their collection

Outcome: Incident HF, HFpEF and HFrEF starting in V5 and extending through available follow-up.

Exposure (V5): 128 aptamers for HF; 15 aptamers for HFpEF; 12 aptamers for HFrEF.

Covariates (V5): age, sex, body mass index (BMI), smoking (current, ever, never), systolic blood pressure, antihypertensive treatment, diabetes, total cholesterol, HDL cholesterol, prevalent myocardial infarction (MI), intercurrent myocardial infarction (V5 through date of incident HF event), estimated glomerular filtration rate (eGFR).

d) summary of data analysis

The association between individual aptamers and their corresponding outcomes will be assessed using Cox proportional hazards models. The proportional hazards assumption will be tested by evaluation of Schoenfeld residuals and by interaction of aptamer by time. A main model will be fit including the following covariates: age, sex, BMI, smoking (current, ever, never), systolic blood pressure, antihypertensive treatment, diabetes, total cholesterol, HDL cholesterol, prevalent MI, intercurrent MI, and eGFR.

e) Any anticipated methodologic limitations or challenges if present

None are anticipated

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ 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 is distributed to ARIC PIs annually, 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 or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□X Publications□ X Proposal Search]

☒ Yes ☐ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11.

Shah AM, Myhre PL, Arthur V, Dorbala P, Rasheed H, Buckley LF, Claggett B, Liu G, Ma J, Nguyen NQ, et al. Large scale plasma proteomics identifies novel proteins and protein networks associated with heart failure development. *Nature Communications*. 2024;15:528.

Ramonfaur D, Buckley LF, Arthur V, Yang Y, Claggett BL, Ndumele CE, Walker KA, Austin T, Odden MC, Floyd JS, et al. High Throughput Plasma Proteomics and Risk of Heart Failure and Frailty in Late Life. *JAMA Cardiology*. 2024;9:649-658.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ Yes ☐ No → Skip to question 12

11.b. If yes to 11.a., is the proposal

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* 2015.34; 2017.27, 2018.19

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website□Publications□Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References: 1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart Disease and Stroke Statistics-2021

Update: A Report From the American Heart Association. *Circulation*. 2021;143:e254-e743. doi: 10.1161/CIR.0000000000000950
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. *Journal of the American College of Cardiology*. 2013;62:e147-e239. doi: 10.1016/j.jacc.2013.05.019
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2016;37:2129-2200. doi: 10.1093/eurheartj/ehw128
4. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, Devore AD, Yancy CW, Fonarow GC. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol*. 2017;70:2476-2486. doi: 10.1016/j.jacc.2017.08.074
5. Braunwald E. Heart failure. *JACC Heart Fail*. 2013;1:1-20. doi: 10.1016/j.jchf.2012.10.002
6. Lekavich CL, Barksdale DJ, Neelon V, Wu JR. Heart failure preserved ejection fraction (HFpEF): an integrated and strategic review. *Heart Fail Rev*. 2015;20:643-653. doi: 10.1007/s10741-015-9506-7
7. Xiang B, Zhang R, Wu X, Zhou X. Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis. *JAMA Netw Open*. 2022;5:e2231963. doi: 10.1001/jamanetworkopen.2022.31963
8. Smith JG, Gerszten RE. Emerging Affinity-Based Proteomic Technologies for Large-Scale Plasma Profiling in Cardiovascular Disease. *Circulation*. 2017;135:1651-1664. doi: 10.1161/CIRCULATIONAHA.116.025446
9. Suhre K, McCarthy MI, Schwenk JM. Genetics meets proteomics: perspectives for large population-based studies. *Nat Rev Genet*. 2021;22:19-37. doi: 10.1038/s41576-020-0268-2
10. Finan C, Gaulton A, Kruger FA, Lumbers RT, Shah T, Engmann J, Galver L, Kelley R, Karlsson A, Santos R, et al. The druggable genome and support for target identification and validation in drug development. *Sci Transl Med*. 2017;9. doi: 10.1126/scitranslmed.aag1166
11. Burgess S, Foley CN, Zuber V. Inferring Causal Relationships Between Risk Factors and Outcomes from Genome-Wide Association Study Data. *Annu Rev Genomics Hum Genet*. 2018;19:303-327. doi: 10.1146/annurev-genom-083117-021731
12. Schmidt AF, Finan C, Gordillo-Marañón M, Asselbergs FW, Freitag DF, Patel RS, Tyl B, Chopade S, Faraway R, Zwierzyna M, et al. Genetic drug target validation using Mendelian randomisation. *Nat Commun*. 2020;11:3255. doi: 10.1038/s41467-020-16969-0
13. Ferreira JP, Verdonschot J, Collier T, Wang P, Pizard A, Bär C, Björkman J, Boccanelli A, Butler J, Clark A, et al. Proteomic Bioprofiles and Mechanistic Pathways of Progression to Heart Failure: The HOMAGE Study. *Circ: Heart Failure*. 2019;12:e005897. doi: 10.1161/CIRCHEARTFAILURE.118.005897
14. Stenemo M, Nowak C, Byberg L, Sundström J, Giedraitis V, Lind L, Ingelsson E, Fall T, Ärnlöv J. Circulating proteins as predictors of incident heart failure in the elderly: Circulating proteins as predictors of incident heart failure. *European Journal of Heart Failure*. 2018;20:55-62. doi: 10.1002/ejhf.980
15. Nayor M, Short MI, Rasheed H, Lin H, Jonasson C, Yang Q, Hveem K, Felix JF, Morrison AC, Wild PS, et al. Aptamer-Based Proteomic Platform Identifies Novel Protein Predictors of Incident Heart Failure and Echocardiographic Traits. *Circ: Heart Failure*. 2020;13:e006749. doi: 10.1161/CIRCHEARTFAILURE.119.006749
16. Egerstedt A, Berntsson J, Smith ML, Gidlöf O, Nilsson R, Benson M, Wells QS, Celik S, Lejonberg C, Farrell L, et al. Profiling of the plasma proteome across different stages of human heart failure. *Nature Communications*. 2019;10:5830. doi: 10.1038/s41467-019-13306-y

17. Shah AM, Myhre PL, Arthur V, Dorbala P, Rasheed H, Buckley LF, Claggett B, Liu G, Ma J, Nguyen NQ, et al. Large scale plasma proteomics identifies novel proteins and protein networks associated with heart failure development. *Nat Commun*. 2024;15:528. doi: 10.1038/s41467-023-44680-3
18. Ramonfaur D, Buckley LF, Arthur V, Yang Y, Claggett BL, Ndumele CE, Walker KA, Austin T, Odden MC, Floyd JS, et al. High Throughput Plasma Proteomics and Risk of Heart Failure and Frailty in Late Life. *JAMA Cardiol*. 2024;9:649-658. doi: 10.1001/jamacardio.2024.1178
19. Henry A, Mo X, Finan C, Chaffin MD, Speed D, Issa H, Denaxas S, Ware JS, Zheng SL, Malarstig A, et al. Mapping the aetiological foundations of the heart failure spectrum using human genetics. *medRxiv*. 2023:2023.2010.2001.23296379. doi: 10.1101/2023.10.01.23296379

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