**APPENDIX 1: Internal Manuscript Concept Sheet**

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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT461 |
| **Submission Date** | 10/26/22 |
| **Project Title** | Association of rs5491 with heart failure in the eMERGE Network |
| **Tentative Lead Investigator** *(first author)* | Ravi B. Patel |
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| **Tentative Senior Author** *(last author)* | Laura Rasmussen-Torvik PhD |
| **All Other Authors**  | Ravi V. Shah, Shilin Zhao, Theresa Walunas, Megan Roy-Puckelwartz, Jennifer A. Pacheco, Elizabeth M. McNally, Sanjiv J. Shah, any other coauthors are welcome |
| **Sites Participating** | All sites are welcome |
| **Background / Significance** | Intercellular adhesion molecule-1 (ICAM-1) is a cell surface protein that participates in endothelial activation and is hypothesized to play a central role in heart failure (HF). Using 3 prospective NHLBI cohorts, we have previously evaluated the associations of pre-specified missense genetic variants of *ICAM1* with circulating ICAM-1 levels and incident HF. One missense variant (rs5491) was common in Black participants, but rare in other race/ethnic groups. This variant was associated higher ICAM-1 levels at 2 timepoints. rs5491 was also associated with increased risk of HF with preserved ejection fraction in our primary cohort and with overall HF in validation.  |
| **Outline of Project** | We propose to evaluate the association of rs5491 with HF by ICD9/10 code among African American participants of eMERGE. The results of such an analysis offer important supplementary information to that which we have previously shown in NHLBI cohort populations. Specifically, eMERGE is a more diverse cohort, and it is important to understand if our previous findings extend to broader populations. |
| **Desired Data - Common Variables\*** *(Available from the CC)* | X Demographics X ICD9/10 codesX CPT codesX PhecodesX BMI | ☐ Common Variable Labs☐ Common Variable Meds☐ Geocoding 2015 ACS variables☐Other: Case/Control status  |
| **Other Desired Data *(Available from participating sites)*** | *Please specifically list out any data elements that participating sites would collect or extract from clinical or other sources for this project (i.e. not common variables above)* *N/A* |
| **Desired Genetic Data** | X eMERGE I-III Merged set (HRC imputed, GWAS)X eMERGE PGx/PGRNseq data set ☐eMERGEseq data set (Phase III)☐eMERGE Whole Genome sequencing data set☐eMERGE Exome chip data set☐eMERGE Whole Exome sequencing data set☐Other (not listed above): |
| **Does project pertain to an existing eMERGE Phenotype?** | ☐Yes, if so please list X No |
| **Planned Statistical Analyses** | This analysis consist of individuals of self identified Black or African American race/ethnicity given that the MAF of rs5491 is >20% in such cohorts, but rare in other race/ethnic groups. We will model the presence of rs5491 using dosage form (additive model). We will perform logistic regression to evaluate the association of rs5491 with HF by ICD 9/10 code. We will adjust for age, sex, and the first 3 principal components of ancestry.  |
| **Ethical Considerations** | N/A |
| **Target Journal** | Circulation Heart Failure as a Research Letter or Brief Report |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | Fall 2022 – obtain approvalWinter 2022- statistical analysis and manuscript draftingSpring 2022 – obtain approval and submit |

***\*\**** *This section should include the timeline for completion of project, including: approval, project duration, first and second draft of the paper and submission.*