**APPENDIX 1: Internal Manuscript Concept Sheet**

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| **eMERGE Network: Manuscript Concept Sheet** | | |
| **Reference Number**  *(to be assigned by CC)* | NT454 | |
| **Submission Date** | June 30, 2022 | |
| **Project Title** | Shared Genetic Architecture of RV structure and metabolic traits | |
| **Tentative Lead Investigator** *(first author)* | Vineet Agrawal | |
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| **Tentative Senior Author**  *(last author)* | Jonathan D. Mosley (jonathan.d.mosley@vumc.org) | |
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| **Sites Participating** | Vanderbilt University Medical Center | |
| **Background / Significance** | Right ventricular (RV) failure is both underrecognized and highly morbid, and unlike other causes of heart failure, there are no RV specific causes. We do not understand what factors drive progression of RV dilation and reduction in function, but genomic approaches may identify both molecular/genetic targets as well as clinical diagonoses that may play an important modulatory role in RV dysfunction. | |
| **Outline of Project** | This project will investigate the genetic architecture underlying an echocardiographic measure of RV structure (RV diameter in a parasternal long axis view). We will use eMERGE network as a secondary data source to conduct a phenome-wide association study using a polygenic score for RV diameter that we have created to identify clinical conditions that may share genetic architecture with RV structure. We plan to validate any associations using 2-sample Mendelian randomization, as well as externally validate these associations with an alternate source of RV structure measurements in the MESA study (available through dbGaP in the MESA-RV study). | |
| **Desired Data - Common Variables\***  *(Available from the CC)* | Demographics  ICD9/10 codes  ☐CPT codes  ☐Phecodes  ☐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)* | |
| **Desired Genetic Data** | Check mark, Wingdings font, character code 252 decimal.eMERGE I-III Merged set (HRC imputed, GWAS)  ☐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): PheWAS data | |
| **Does project pertain to an existing eMERGE Phenotype?** | ☐Yes, if so please list  No | |
| **Planned Statistical Analyses** | Bayesian sparse linear mixed model to generate a polygenic score for RV diameter measurement, adjusted for age, sex, and 5 prinicipal components. Logistic regression for PheWAS. Inverse variance weighted meta-analysis, Egger analysis, and Weighted median analysis for Mendelian randomization. | |
| **Ethical Considerations** | All data will be de-identified and aggregated, thus posing no ethical concerns. | |
| **Target Journal** | Circulation Heart Failure | |
| **Milestones**  *(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | July 31, 2022 – Approval  Project duration – 2 months or sooner  Draft completion – by 6 months (September 31, 2022) or sooner  Submission – by December 31, 2022 or sooner | |

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