|  |
| --- |
| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT458 |
| **Submission Date** | 8/1/2022  |
| **Project Title** | Polygenic associations with sudden death in the young |
| **Tentative Lead Investigator** *(first author)* | Gregory Webster |
| **Tentative Lead Investigator Email Address** | rgwebster@luriechildrens.org |
| **Tentative Senior Author** *(last author)* | Adam Gordon |
| **All Other Authors**  | Christina Laternser, Alfred L. George Jr., Elizabeth McNally, Megan Roy-Puckelwartz |
| **Sites Participating** | Current participants: Northwestern UniversityOpen to all sites |
| **Background / Significance** | Postmortem genetic testing of young individuals with sudden death has previously identified pathogenic gene variants. However, most prior studies considered highly penetrant monogenic variants. Common variant analysis in sudden death has mostly focused on adults at risk for coronary artery disease. Neither paradigm has sufficiently explained the genetic architecture of sudden death in young individuals; however, existing polygenic risk scores for cardiac disease can potentially help bridge the gap between these two approaches. We seek to explore this possibility using our established cohort of decedents under 45 years of age with detailed genotype and phenotype information. |
| **Outline of Project** | We have calculated existing polygenic risk scores for cardiac conditions (PGScatalog.org) in our cohort of sudden death in the young. We will calculate these same scores within the eMERGE I-III merged dataset, excluding those with cardiac conditions, as a population reference cohort. We will compare scores in our previously established case cohort to this population reference to explore the scores’ utility in predicting or refining risk for sudden death.  |
| **Desired Data - Common Variables\*** *(Available from the CC)* | [x] Demographics [x] ICD9/10 codes[x] CPT codes[x] Phecodes[x] BMI | [x] Common Variable Labs[x] Common Variable Meds[ ]  Geocoding 2015 ACS variables[x] 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** | [x] eMERGE I-III Merged set (HRC imputed, GWAS)[ ] eMERGE PGx/PGRNseq data set [ ] eMERGEseq data set (Phase III)[x] 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?** | [x] Yes, if so please list: we will leverage existing, EHR-derived eMERGE case/control status for cardiac diseases as potential exclusions from our control cohort. [ ] No |
| **Planned Statistical Analyses** | Comparison of existing polygenic risk scores for cardiac disease between phenotype-defined cases and controls using loci extracted from WGS or genotyping data. |
| **Ethical Considerations** | None |
| **Target Journal** | Will be determined by the results, but anticipate an AHA journal. |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | Gather data from coordinating center: 09/01/2022Conduct statistical analyses: 12/1/2022Write manuscript: 1/1/2023Circulate and submit manuscript: 2/1/2023 |

**\*Common Variables available across all datasets:**

* Demographics: sex, year of birth, decade of birth, race, ethnicity
* Codes: (repeated values & age at event): ICD, CPT, Phecodes
* BMI: (repeated value & age at event) height, weight, BMI
* Labs: (lab name, repeated lab value & age at event) Serum total cholesterol, LDL, HDL, Triglycerides, Glucose fasting/non-fasting/unknown, & White Blood Cell count
* Medications: (medication name, repeated, & age at event) Cerivastatin sodium, Rosuvastatin, Simvastatin, Fluvastatin, Pravastatin, Lovastatin, Atorvastatin, & Pitavastatin
* Other: Case/Control status on Phase I and Phase II phenotype: only on GWAS dataset participants