|  |  |  |
| --- | --- | --- |
| **eMERGE Network: Manuscript Concept Sheet** | | |
| **Reference Number**  *(to be assigned by CC)* | NT311 | |
| **Submission Date** | 10/30/2018 | |
| **Project Title** | Penetrance and outcome of pulmonary hypertension associated with germline BMPR2 mutations in a population based cohort | |
| **Tentative Lead Investigator** *(first author)* | Na Zhu/ Carrie Welch | |
| **Tentative Senior Author**  *(last author)* | Wendy Chung | |
| **All Other Authors** | Yufeng Shen, Chunhua Weng, Cong Liu | |
| **Sites Participating** | Any other interested eMERGE sites | |
| **Background / Significance** | Pulmonary arterial hypertension (PAH) is a rare, progressive and often lethal disorder disproportionately afflicting women. Approximately 20% of idiopathic PAH and 60-80% of familial PAH is due to mutations in BMPR2. Prior data suggests that the lifetime penetrance of BMPR2 mutations is ~ 20% for men and ~ 40% for women, but prior studies have been biased by the ascertainment of symptomatic individuals or those with a family history of PAH. Population based ascertainment would give us a more accurate estimate of penetrance in the general population. | |
| **Outline of Project** | Our goal is to use the eMERGE cohort that is currently under full sequence analysis for BMPR2 to study the penetrance and outcome of PAH in a less biased cohort. We will group rare variants in BMPR2 by predicted pathogenicity, and investigate the penetrance and outcome of each group of variants. | |
| **Desired Data - Common Variables\***  *(Available from the CC)* | Demographics  ICD9/10 codes  CPT codes  Phecodes  BMI | Common Variable Labs  Common Variable Meds  Other: Case/Control status on Phase I and Phase II phenotypes |
| **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)*  Family history of PAH or sudden death  PAH diagnosis (and any other cardiac or respiratory diagnosis), syncope, exercise intolerance  Echocardiogram results of tricuspid regurgitation or right heart failure  Right heart catheterization results | |
| **Desired Genetic Data** | 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): | |
| **Does project pertain to an existing eMERGE Phenotype?** | Yes, if so please list  No | |
| **Planned Statistical Analyses** | Determine age related PAH penetrance associated with mutations in BMPR2 and assess symptoms for potentially undiagnosed PAH in mutation carriers | |
| **Ethical Considerations** | None | |
| **Target Journal** | Chest | |
| **Milestones**  *(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | 12/1/18: study approval  1/1/19: delivery of genetic data  3/1/19: delivery of clinical data  6/15/19: first draft of paper  8/15/19: second draft of paper  10/15/19: submission of manuscript | |

**\*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