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| **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)* | [x] Demographics [x] ICD9/10 codes[x] CPT codes[x] Phecodes[x] 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 deathPAH diagnosis (and any other cardiac or respiratory diagnosis), syncope, exercise intoleranceEchocardiogram results of tricuspid regurgitation or right heart failureRight heart catheterization results |
| **Desired Genetic Data** | [ ] eMERGE I-III Merged set (HRC imputed, GWAS)[ ] eMERGE PGx/PGRNseq data set [x] 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** | 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 approval1/1/19: delivery of genetic data3/1/19: delivery of clinical data6/15/19: first draft of paper8/15/19: second draft of paper10/15/19: 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