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| **eMERGE Network: Manuscript Concept Sheet** | | |
| **Reference Number**  *(to be assigned by CC)* | NT415 | |
| **Submission Date** | 12/14/2020 | |
| **Project Title** | Pathogenic Variants in Aortopathy Related Genes in the eMERGE Network: Prevalence, Clinical Correlates and Outcomes. | |
| **Tentative Lead Investigator** *(first author)* | Omar Elsekaily | |
| **Tentative Senior Author**  *(last author)* | Iftikhar Kullo | |
| **All Other Authors** | other eMERGE investigators | |
| **Sites Participating** | Mayo, other eMERGE sites | |
| **Background / Significance** | . The American College of Medical Genetics and Genomics (ACMG) has recommended the return of P/LP variants in several aortopathy-related genes since detection of these conditions may enable life-saving medical interventions. However, in the context of large population sequencing programs, the prevalence, penetrance, and clinical correlates of such variants are unclear. | |
| **Outline of Project** | Aim 1). Prevalence. We will calculate the prevalence of aortopathy-related P/LP variants among the 25,000 participants in phase III of the eMERGE network.  Aim 2). Outcomes. We will evaluate whether the return of results led to clinical actions related to the returned results. Outcomes measured include referral to a specialist, new diagnosis of aortopathy or related disorders, new tests related to RoR, changes in medications and treatment, and periodic surveillance initiation.  Aim 1). Penetrance. Due to the heterogeneity of clinical features among disorders associated with aortopathy, we will deem the variant as ‘penetrant’ if the patient had received a clinical diagnosis of the returned variant either pre- or post- RoR. This is based on the assumption that participants will only receive a clinical diagnosis if they meet specific clinical criteria. We will also ascertain the highest aortic root diameter in the EHR and calculate Z-scores. If the Z-score is greater than 2, we will also deem the P/LP variant as ‘penetrant’. | |
| **Desired Data - Common Variables\***  *(Available from the CC)* | Demographics  ICD9/10 codes  CPT codes  Phecodes  BMI | Common Variable Labs  Common Variable Meds  Other: Aortic root measurements |
| **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** | 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** | Data will be collected from eMERGE sites using Data Freeze 3, as well as data derived from an addended aortopathy form. Analyses will be performed relevant to each of the three proposed specific aims. | |
| **Ethical Considerations** | None | |
| **Target Journal** | GIM (brief report). | |
| **Milestones**  *(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | * Dec- Jan 2021: Obtain aortopathy data from Data Freeze 3, submit network addendum for aortopathy form * Feb- 2021: Process and analyze data across the eMERGE network * March 2021: Circulate draft of the manuscript * April 2021: Submit manuscript draft for peer review, publication | |