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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT376 |
| **Submission Date** | 2/12/2020 |
| **Project Title** | Heterozygous FH in the eMERGE Network: Penetrance, Outcomes and Cardiovascular Risk. |
| **Tentative Lead Investigator** *(first author)* | Ozan Dikilitas |
| **Tentative Senior Author** *(last author)* | Iftikhar Kullo |
| **All Other Authors**  | David Kochan, Scott Hebbring, Daniel Schaid, Marc Williams, Gail Jarvik, Heidi Rehm, Eric Venner, Hana Zouk, Richard Gibbs, Josh Peterson, Jodell Jackson, Richard Sharp, Teri Manolio, other investigators |
| **Sites Participating** | Mayo, other eMERGE sites |
| **Background / Significance** | FH is a relatively common, CDC Tier 1 autosomal dominant disorder that is associated with markedly increased risk of premature CHD. We propose to study penetrance, outcomes and cardiovascular risk in 163 adult heterozygous FH patients, identified as part of the eMERGE Network’s eMERGEseq study.  |
| **Outline of Project** | Aim 1). Penetrance. This analysis will be limited to individuals who were not recruited on the basis of hyperlipidemia. We will ascertain the highest LDL-C level in the EHR and if this is greater than 155 mg/dl, deem the P/LP variant as ‘penetrant’. If the patient is on a lipid-lowering medication, we will deem the variant as ‘penetrant’ but also impute ‘true’ LDL-C based on statin type and dose.Aim 2). Outcomes. We will assess whether return of results led to meaningful changes in clinical intervention and lipid management. Outcomes measured include new diagnosis of FH, new tests ordered, changes in medications and treatment, and measurement of LDL-C subsequent to return of results. Aim 3). Cardiovascular risk. We will calculate odds of having CHD in patients with P/LP FH variants, compared to a) age, sex, site (if possible) and EHR depth matched individuals with normal LDL-C levels (<130 mg/dL) and b) age, sex, LDL-C, site (if possible) and EHR depth matched individuals. |
| **Desired Data - Common Variables\*** *(Available from the CC)* | [ ] Demographics [x] ICD9/10 codes[x] CPT codes[ ] Phecodes[ ] BMI  | [x] Common Variable Labs[x] 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)*  |
| **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** | Data will be aggregated from eMERGE sites using 6-month outcomes from Data Freeze 2, as well as data derived from an addended FH Outcomes form. CHD will be ascertained based on previously validated algorithms. Analyses will be performed relevant to each of the three proposed specific aims.  |
| **Ethical Considerations** | None |
| **Target Journal** | Circulation |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | * Feb 2020: Obtain FH outcomes data from Data Freeze 2, submit network addendum for FH Outcomes form
* February-March 2020: Process and analyze FH outcomes data across the eMERGE network
* April 2020: Circulate draft of the manuscript
* May 2020: Submit manuscript draft for peer review, publication
* June 2020: Publish manuscript
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