**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Submission Date** | May 6, 2015 |
| **Project Title** | A phenome-wide association study to discover pleiotropic effects of *PCSK9*. |
| **Tentative Lead Investigator (first author)** | Maya S. Safarova |
| **Tentative Senior Author (last author)** | Iftikhar J. Kullo |
| **All other authors** | Erin Austin, Mariza de Andrade, Daniel Schaid, Josh Denny  Representation from eMERGE sites |
| **Sites Involved** | All sites |
| **Background / Significance** | Recent animal and genetic studies implicate PCSK9 in the regulation of blood pressure and triglyceride-rich lipoprotein metabolism, suggesting that genetic variants in *PCSK9* are likely to have pleiotropic effects. Given that drugs targeting PCSK9 are expected to be in clinical use in the near future motivates an investigation of associations of *PCSK9* variations with diverse phenotypes in the eMERGE Network. Hitherto, limited data exist on potential pleiotropic effects of *PSCK9* variants. |
| **Outline of Project** | Step 1. Scan for associations between genotyped and imputed *PCSK9* SNPs and EHR-derived clinical phenotypes (PheWAS codes) in patients from the eMERGE Network.  Step 2. Replicate significant pleiotropic associations in an independent cohort of 10,000 individuals from Mayo VDB  Step 3. Perform a combined analysis of results from Aims I and II |
| **Desired**  **Variables (essential for analysis**  **indicated by \*)** | * Institution * Number of patients with measured *PCSK9* variants * Baseline clinical characteristics (age, gender, race, ethnicity, current smoking, hypertension, diabetes, BMI) * Genotyping platform * Lipid panel (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, lipoprotein(a)) * The most recent statin mention prior to date of blood test (statin type and dose) * PheWAS codes |
| **Desired data** | * All genotyped and imputed data for *PCSK9* * Case-control status via application of PheWAS algorithm |
| **Planned Statistical Analyses** | The QC and data analysis will be conducted using a combination of PLINK and the R statistical package, including R PheWAS package. All PCSK9 SNPs (common and rare) will be analyzed for associations using both single point and agglomerative tests. To control for both population stratification and close relationships the “pedgene” software will be used. |
| **Ethical considerations** | None |
| **Target Journal** | Circulation: Cardiovascular Genetics |
| **Milestones\*\*** | May 2015: Obtain information from all sites  June 2015: Conduct data review and analysis.  July 1, 2015: First draft of manuscript circulated  July 25, 2015: Second draft of manuscript circulated  August 30, 2015: Manuscript submission |

***\*\**** *This section should include: Timeline for completion of project, including approval, project duration, first and second draft of the paper and submission.*