**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Reference Number** | NT269 |
| **Submission Date** | 01/29/2018 |
| **Project Title** | **Common and rare variant association of Opiod Addiction using the network-wide eMERGE 3 cohort** |
| **Tentative Lead Investigator (first author)** | Shawn Murphy |
| **Tentative Senior Author (last author)** | Scott T.Weiss |
| **All other authors** | Su Chu, Beth Karlson, Jordan Smoller, Victor Castro  *Any additional eMERGE 3 members interested in participating* |
| **Sites Involved** | We propose a network-wide study of opioid addiction and related phenotypes derived from the ICD 9 codes (all sites invited to participate). |
| **Background / Significance** | The US is in the midst of an epidemic of opiod addiction. To date there are no known stuides of the geneitcs of opoid addiction. We are looking to investigate the use of opiates in addictive patterns based on the EMR and relate them to the eMERGE GWAS data. The addictive patterns phenotypes will be defined from the EHR data both structured and unstructured, using the OMOP formulation of the data model. One phenotype will be patients with opiates administered to treat (short term) surgical pain who have no history of opiate abuse but who remain on opiates for a year (uninterrupted) since their surgery. Controls would be those who stop opiates within 1 month of their operation. |
| **Outline of Project** | The project will involve the following steps:   1. Selection of Opioid addiction phenotypes by temporal algorithms that use ICD, Procedure, and Medication codes. 2. Perform GWAS on Opioid addiction phenotypes using eMERGE network-wide imputed GWAS data. 3. Identify major common and disease-specific opioid addiction variants in terms of effect size and population attributable risk 4. Manuscript preparation and submission |
| **Desired**  **Variables**  **(essential for analysis**  **indicated by \*)** | This study involves GWAS analysis of ICD, procedure, and medication codes for Opioid Addiction among all EMERGE participants. The required variables include (with relative temporal designations):   * ICD9 codes for Opioid Addiction network-wide\*, specifically for phenotypes relevant for incident Opioid Abuse * Surgical procedure codes * Codes for opiate medications. * Imputed GWAS data * adjustment covariates including the following: Age, sex, race/ethnicity, cohort/site\*, medication use, smoking status, BMI, among others. |
| **Desired Data** | * Imputed genome-wide genotypes * Genetic ancestry information (for ancestry adjustment in GWAS). |
| **etPlanned Statistical Analyses** | We will focus on ICD, Procedure, and Medication codes related to opiate addiction data (and controls). We will also obtain the relevant covariates for those patients using the EHR. We will assess the genetic associations with respiratory phenotypes using a multi-faceted approach:  1) We will perform a GWAS using Opioid phenotypes and the eMERGE3 imputed network-wide genotypes for both rare and common variants.  2) We will describe their genetic effect in terms of effect size and population attributable risk, and examine shared phenotypic associations with the various Opioid-relevant phenotypes. |
| **Ethical considerations** | We will not use restricted notes from drug abuse programs and councilors as designated by Federal and State law. The EMR and genomic data will be stored at a secured location in the data storage system at Partners Healthcare. No data will be shared with unauthorized third parties. Patient identity will not be compromised by the proposed analysis. We will also abide by the eMERGE guidelines in this regard. |
| **Target Journal** | To be determined |
| **Milestones\*\*** | 1. May 2018 validation of Harvard addiction algorithm complete. 2. August 2018: GWAS analysis for Opioid Addiction and related phenotypes defined by ICD9 codes 3. September 2018: Implementation of Opioid Addiction computed phenotype throughout the network 4. Jan 2019: GWAS analysis for computed Opioid Addiction phenotypes 5. February 2019 Rare variant analysis of Opioid Addiction phenotype 6. March 2019: Further assessment of Opioid Addiction genes via genetic effect size and population attributable risk measurement. 7. March 2019: Manuscript preparation 8. June 2019: Draft of first submission |

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