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| **eMERGE Network: Proposal for Analysis**Project/Manuscript Concept Sheet |
| **Reference Number** | NT290 |
| **Submission Date** | May 22, 2018 |
| **Project Title** | Genetic Risk Factors for Intracerebral Hemorrhage and Subarachnoid Hemorrhage: A Meta-Analysis of Genome-Wide Association Studies |
| **Tentative Lead Investigator** *(first author)* | Sarah Pendergrass, Geisinger (spendergrass@geisinger.edu) |
| **Tentative Senior Authors** *(last author)* | Contributing to meta-analysis from many sites, thus senior authors for the meta-analysis are Liam Gaziano, Adam Butterworth, John Danesh, from University of Cambridge  |
| **All Other Authors**  | Marc Williams, Geisinger |
| **Sites Involved** | Geisinger |
| **Background / Significance** | * We are collaborating on a meta-analysis to identify variants associated with hemorrhagic stroke and its subtypes, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH).
* The largest published GWAS on ICH (Woo et al. 2014) included 1,545 cases and 1481 controls. It found no variants associated with total ICH at the genome-wide significance threshold, but did find one locus associated with lobar ICH, and another locus associated with non-lobar ICH.
* Heritability studies have identified a genetic contribution to ICH (Devan et al. 2013; Rost, Greenberg, and Rosand 2008)
* The collaborative project we are undertaking, which consists of multiple-fold more cases than the previous GWAS, has the potential to identify multiple novel loci that surpass genome-wide significance
* This is also true for SAH, which displays some familial aggregation, where no large-scale GWAS has been conducted
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| **Outline of Project** | * With data from MVP, EPIC-CVD, and other biobanks we contacted so far, we have accumulated about 6,500 cases of ICH and 3600 cases of SAH (not including Geisinger, or eMERGE)
	+ *Note, this will be eMERGE contributing association results to a large multi-site meta-analysis, and thus there will be many authors on the resultant manuscript. No sharing of individual genetic or phenotypic information from eMERGE will occur.*
* This meta-analysis will be bigger than the largest published GWAS on intracerebral hemorrhage by several fold, and no GWAS has been done on subarachnoid hemorrhage before
* We propose to perform a GWAS for ICH and SAH using ICD-9 and ICD-10 codes for case/control status, using the eMERGE III imputed dataset. The results of these associations will contribute to this larger ICH and SAH meta-analysis
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| **Desired Variables** *(essential for analysis**indicated by* ***\*****)* | AgeSexBMIGenetically informed ancestry from principle componentsICD Codes |
| **Desired Data** | Emerge I-III imputed data |
| **Planned Statistical Analyses** | Quality control for the imputed data, including imputation score cutoff and minor allele frequency (MAF) cutoff > 1%. We will drop out from the eMERGE samples any that are in the current MyCode Community Health Initiative array based data we are using at Geisinger, as we are also calculating associations for ICH and SAH within MyCodeLogistic regression and analyses will be adjusted for age, sex, and the number of principle components to account for ancestry.Analyses will also be adjusted for age, sex, BMI, and principle components to identify the shift in associations when incorporating BMI as a covariateWe may employ linear mixed models to account for relatedness between samples. We will share the resultant association results to contribute to the larger meta -analysisNo individual level genetic or phenotypic data will be shared with external collaborators on this project.  |
| **Ethical Considerations** | All data will be de-identified, and only summary data will be shared in resultant manuscripts |
| **Target Journal** | PLOS Medicine, American (or European) Journal of Human Genetics  |
| **Milestones\*\*** | July 2018 for completion of analyses, early Fall 2018 manuscript draft completed. Fall 2018 submission of paper.  |

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