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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT385 |
| **Submission Date** | 4/6/2020 |
| **Project Title** | Genetics and pleiotropy of antinuclear antibodies and its contribution in lupus  |
| **Tentative Lead Investigator** *(first author)* | Vivian Kawai |
| **Tentative Senior Author** *(last author)* | Jonathan Mosley, C. Michael Stein |
| **All Other Authors**  | Qiping Feng, WeiQi Wei, Cecilia P. Chung, Ge Liu, Thomas Lasko, Jacy Zanussi, Nancy J. Cox, Nancy Olsen |
| **Sites Participating** | Current participants: Vanderbilt Open to all sites |
| **Background / Significance** | Antinuclear antibodies (ANA) are antibodies that react against self-antigens and are commonly used to help diagnose systemic lupus erythematosus (SLE). Because the test is positive (ANA+) in almost every patient with SLE, ANA+ is considered virtually a requisite for the diagnosis of SLE. However, the test is also positive in a large proportion of the general population (~20%). Although very few of these ANA+ individuals will develop an autoimmune disease in the future, the clinical impact of ANA+ in people without autoimmune disease is unknown. A second problem is that the common occurrence of ANA+ in people without autoimmune disease can lead to an incorrect diagnosis of SLE. To more accurately diagnose SLE and prevent false diagnoses, we need to address two major knowledge gaps: 1) we need to understand the importance of a positive ANA test in people without an autoimmune disease; and 2) we need to be able to predict which people with a positive ANA test have or will develop SLE. |
| **Outline of Project** | To define the clinical importance of ANA+ and its relationship with SLE, we will:1. Perform a PheWAS using ANA+ and a genetic risk score (GRS) for ANA+ to test for association with clinical phenotypes in the electronic health records (EHRs). In addition, we will also perform a PheWAS to look for associations between genetic liability for SLE and clinical phenotypes using a GRS for SLE.
2. Create a phenotype risk score for SLE using clinical information from the EHRs and machine learning techniques
3. Combine clinical information and genetic information for ANA+ and SLE to develop a predictive model for SLE.

We will conduct the discovery analyses in BioVU, followed by replication in eMERGE.  |
| **Desired Data - Common Variables\*** *(Available from the CC)* | [x] Demographics [x] ICD9/10 codes[ ] CPT codes[x] Phecodes[ ] BMI | [x] Common Variable Labs[x] Common Variable Meds[x] Other: Case/Control status on Phase I and [x] Phase II phenotypes |
| **Other Desired Data *(Available from participating sites)*** |  |
| **Desired Genetic Data** | [x] 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 [x] No |
| **Planned Statistical Analyses** | PheWAS, validation of significant hits on GWAS for ANA+ |
| **Ethical Considerations** | None |
| **Target Journal** | Depend on the results  |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | Gather data from coordinating center: 04/01/2021Conduct statistical analyses: 04/12/2021Write manuscript: 04/06/2022Circulate and submit manuscript: 06/06/2022  |