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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT422 |
| **Submission Date** | 03/30/2021 |
| **Project Title** | Comprehensive evaluation of the role of PUFA metabolism and complex disease risk  |
| **Tentative Lead Investigator** *(first author)* | Elizabeth Jasper, Nikhil K. Khankari |
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| **Tentative Senior Author** *(last author)* | Digna R. Velez Edwards, Todd L. Edwards |
| **All Other Authors**  | Sarah H. Jones, Jacklyn N. Hellwege |
| **Sites Participating** | Open to all sitesCurrent participants:Vanderbilt  |
| **Background / Significance** | There are multiple known relationships between polyunsaturated (PUFA) metabolism and complex disease, including cancer and adverse pregnancy outcomes. Metabolism of PUFAs generate an array of eicosanoids, among which some are inflammatory (e.g., prostaglandin E2). Many inflammatory eicosanoids are produced by ω-6 PUFA metabolism, which are competitively inhibited by ω-3 PUFA metabolism. Genome-wide association studies (GWAS) have identified several variants related to circulating PUFA levels (for both ω-6 and ω-3).We propose to utilize eMERGE genotype and phenotype information to address the **primary aim** to identify phenotypes associated with ω-3 and ω-6 PUFAs. We will derive polygenic risk scores (PRSs) for PUFAs using prior GWAS, which will then be subsequently utilized in a Phenome-wide association study (PheWAS) to identify associated clinical phenotypes. We will conduct **secondary analyses** examining the association between PUFA polygenic risk scores (PRSs) and specific cancers and adverse pregnancy outcomes. Results will be independently validated within the BioVU population at Vanderbilt University Medical Center. Given the correlated nature of the exposures, we will also conduct multivariable Mendelian randomization (MR) to examine the causal effects of PUFAs on cancer and pregnancy outcomes. Furthermore, aspirin and NSAIDs share biologic pathways with PUFA metabolism, and thus may influence levels of resulting inflammatory eicosanoids. Therefore, we intend to also examine the influence of aspirin/NSAID use on cancer and pregnancy outcomes. |
| **Outline of Project** | Phenome-wide association studies (PheWAS) will be conducted using PRSs for ω-3 and ω-6 PUFAs in eMERGE. A similar cohort from BioVU will serve as a replication cohort. |
| **Desired Data - Common Variables\*** *(Available from the CC)* | [x] Demographics [ ] ICD9/10 codes[ ] CPT codes[x] Phecodes[x] 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)*** |  |
| **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, Phe-PheWAS, S-PrediXcan, and multivariable Mendelian randomization |
| **Ethical Considerations** | None |
| **Target Journal** | We anticipate 2-3 manuscripts will be generated from this project. The target journal will be dependent upon the focus of the manuscript. |
| **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: April (2021)Conduct statistical analyses: May through October (2021)Write manuscript(s): November (2021) through January (2022)Circulate and submit manuscript: February (2022) |