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| **eMERGE Network: Manuscript Concept Sheet** | | |
| **Reference Number**  *(to be assigned by CC)* | NT421 | |
| **Submission Date** | 04/06/2021 | |
| **Project Title** | Leveraging electronic health record and genomic data to systematically prioritize targets for the treatment of chronic kidney disease complications | |
| **Tentative Lead Investigator** *(first author)* | Jacklyn Hellwege | |
| **Tentative Lead Investigator Email** | jacklyn.hellwege@vumc.org | |
| **Tentative Senior Author**  *(last author)* | Cassianne Robinson-Cohen (Vanderbilt) | |
| **All Other Authors** | Digna Velez Edwards, Todd Edwards, Cecilia Pilar Chung, Wei-Qi Wei | |
| **Sites Participating** | Open to all sites  Current participants: Vanderbilt | |
| **Background / Significance** | Chronic kidney disease (CKD) is associated with several complications which contribute to high morbidity and mortality, and poor quality of life. Treatment decisions for prevention and management of these complications is traditionally and ideally based on evidence from randomized clinical trials (RCTs). However, drug development via RCTs is a lengthy and costly process and the development of interventions for CKD complications has not received adequate investment or interest. Additionally, CKD patients are often excluded from RCTs, for fear of adverse effects or variable efficacy in response to conventional treatments. As a result, uncertainty about the appropriate role for standard therapies in subjects with CKD is rampant and warranted, since those therapies have not been broadly tested on subjects with impaired kidney function. | |
| **Outline of Project** | The goal of this application is to comprehensively survey, evaluate and prioritize genetic targets for the treatment of CKD complications, using genetic and Mendelian randomization (MR) analyses to mimic the putative effects of therapeutic intervention.  Our analyses will be conducted using genomic data, based on Mendelian Randomization methods, and will leverage publicly available genome-wide association data, and data from BioVU, eMERGE and UK BioBank. Using novel techniques and resources, we will 1) interrogate the phenome for putative drug targets for common CKD complications, such as subclinical and clinical cardiovascular disease, metabolic acidosis, anemia and endocrine disruptions, 2) assess the variability in the predicted drug effect according to CKD status and estimated glomerular filtration rate and 3) evaluate the potential for adverse events from current drugs on the market and new drug targets among CKD patients. | |
| **Desired Data - Common Variables\***  *(Available from the CC)* | Demographics  ICD9/10 codes  CPT codes  Phecodes  BMI | Common Variable Labs  Common Variable Meds  Other: Case/Control status on Phase I and Phase II phenotypes |
| **Other Desired Data *(Available from participating sites)*** |  | |
| **Desired Genetic Data** | 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: Chronic Kidney Disease  No | |
| **Planned Statistical Analyses** | GWAS, PheWAS, Mendelian Randomization | |
| **Ethical Considerations** | None | |
| **Target Journal** | Journal of the American Society of Nephrology | |
| **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: 06/2021  Conduct statistical analyses: 08-12/2021  Write manuscript: 01-03/2022  Circulate and submit manuscript: 4/2022 | |