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| **eMERGE Network: Manuscript Concept Sheet** | |
| **Reference Number**  *(to be assigned by CC)* | NT305 |
| **Submission Date** | September 28, 2018 |
| **Project Title** | Genetic variants associated with metformin response and intolerance |
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| **Sites Participating** | All sites |
| **Background / Significance** | Type 2 diabetes mellitus is a major risk factor for cardiovascular disease and highly prevalent. It is estimated that 23.4 million adults in the US have diagnosed diabetes, 7.6 million with undiagnosed diabetes, and 81.6 million with prediabetes. Racial/Ethnic minorities are disproportionally affected by Type 2 diabetes. Compared to whites.2 The resulting health care costs are estimated at $245 billion in 2012, accounting for 1 out of every 5 health care dollars. For reasons of efficacy and cost, metformin is the frontline drug of choice for treating type 2 diabetes. However, it is estimated that there is a 35% failure rate for metformin monotherapy. In addition, serious adverse reactions to metformin are rare (e.g. lactic acidosis (3/100,000) and anemia due to B12 malabsorption) and thus require very large sample sizes. Although we know about pharmacogenomic factors that influence metformin plasma concentration (its pharmacokinetics), much less is known about metformin pharmacodynamic response of diabetic patients to metformin despite its wide use. Metformin is unusual in that it is not metabolized but there is known genomic variants in drug transporters that influence metformin plasma levels and efficacy. In contrast, oral hypoglycemic agents, such as glimepiride glipizide, and glyburide have known interactions with PGx genes. |
| **Outline of Project** | An electronic health record algorithm was developed and implemented at all emerge sites. Outcome measures include the following using an 18 month time window from metformin initiation; time to target hemoglobin A1c (HbA1c) (<7%), lowest HbA1c, and change in HbA1c. We are also evaluating use of metformin in patients with impaired fasting glucose and measurements will focus on the change in HbA1c from baseline. Algorithm has been posted for use on PheKB. |
| **Desired Data - Common Variables\***  *(Available from the CC)* | * Demographics * BMI   Specific metformin response data dictionaries were created and used.  These variables include demographics, allergy notes, and repeated measurements  of fasting and random glucose, hemoglobin A1c, and diabetes medication prescriptions. |
| **Other Desired Data *(Available from participating sites)*** | *Please specifically list out any data elements that participating sites would collect or extract from clinical or other sources for this project (i.e. not common variables above)*  As per the algorithm, sites were asked to send data relating to mention of metformin intolerance in the allergy section of the clinical note. A corresponding data dictionary was provided for this data feature on PheKB. This step was optional as not all sites had easily accessed allergy sections. Thus the resulting analysis of the allergy data is secondary to the genetic analyses of metformin response. |
| **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 - Metformin Response and Intolerance   No |
| **Planned Statistical Analyses** | We will focus on three primary response outcomes in the 18 months following metformin initiation. Participants will be censored at 18 months, metformin discontinuation, or addition of a dual therapy.   1. Target HbA1c (< 7%) 2. Lowest HbA1c 3. Change in HbA1c   For metformin intolerance, we will dichotomize the allergy data (e.g. yes/no for intolerance). We do not anticipate large numbers of intolerance events. However, if sample size is sufficient, as secondary analyses we will explore categories of intolerance (e.g. GI upset, liver injury).  We will perform a genome-wide single-variant association analysis using outcome-appropriate regression modeling (e.g., Cox proportional hazards for time-to-target HbA1c). Analyses will be performed for all common variants with a minor allele frequency greater than 1% that pass relevant quality criteria (e.g., call-rate, imputation quality). Variants will be evaluated under an additive genetic model adjusting for age, sex, BMI, study site, ancestry-informative principal components (PCs) capturing population substructure, and any additional confounding factors (e.g. baseline hemoglobin A1c). If appropriate, race/ethnicity-stratified analyses will be conducted and combined via meta-analysis. We will also perform gene-level aggregate testing of rare variants using the sequence kernel association test (SKAT) using MAF-based weighting and subsetting to variants with predicted functional impact via available annotation resources. |
| **Ethical Considerations** | None |
| **Target Journal** | Diabetes |
| **Milestones**  *(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | Analyses can begin immediately as data is made available. We anticipate a draft of the manuscript by Q1 2019. |