emerge network

eMERGE Network: Manuscript Concept Sheet

Reference Number *(to be assigned by CC)*	NT396
Submission Date	6/29/2020
Project Title	Drug Mendelian randomization analyses to evaluate the effects of ACEI and ARB treatments in SARS-CoV-2 patients
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Sites Participating	Open to all sites Current participants: Vanderbilt
Background / Significance	Reports from China have suggested that outcomes in SARS-CoV-2 patients with hypertension are more severe than normotensive patients. Treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may affect availability of ACE2, a co-receptor for viral entry, and this may in turn affect clinical outcomes in SARS-CoV-2 patients.
Outline of Project	Once SARS-CoV-2 cases have accrued and clinical outcomes are linked to eMERGE genetic data, we will perform association analyses of genetic variants in the AGTR1, ACE, and ACE2 gene regions +/- 1Mb from the transcriptional start and stop sites, adjusted for covariates such as ancestry, age, BMI, and other candidate confounders for SARS-CoV-2 outcomes. We will evaluate outcomes such as death, pneumonia, reduced pulmonary capacity and ventilator use, and other frequently observed clinical complications of SARS-CoV-2 infection. We will also use the summary statistics from our prior and ongoing studies of blood pressure genetics for the genetic variants in the AGTR1, ACE, and ACE2 regions. We have performed genetic association studies of hundreds of thousands of participants in European and African American populations, including unpublished results for the largest study of recent African ancestry participants ever conducted. These summary data will be processed using the method S-PrediXcan, which uses information about genetic effects on gene expression from somatic tissues in concert with summary statistics from genetic association studies to infer relationships between gene expression and traits of interest. Models are developed using an elastic net likelihood penalty, to perform feature selection and estimate weights for genetic variants with a sparseness assumption.

	We will then perform Mendelian randomization analyses of estimates of effects for expressed levels of AGTR1, ACE, and ACE2 by considering SARS-CoV-2 effects in the numerator, and effects on blood pressure in the denominator of the MR ratio. Thereby, we will evaluate SARS-CoV-2 outcomes at the target genes for ACEI and ARB drugs, scaled by the effects on indications for treatment with ARB or ACEI, represented by effects of modifying expression levels of those genes on blood pressure. We will also conduct parallel analyses in the Million Veteran Program study, and the senior investigator of this study, Dr. Edwards, is the co-Chair of the MVP Druggable Genome Working Group.
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)***	COVID outcomes such as hospitalization, pneumonia, admission and time in ICU, intubation and time intubated, death, supplemental oxygen, and other related outcomes.
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: Phecodes and other COVID outcomes ☐ No
Planned Statistical Analyses	1) Association analysis of SNPS for COVID outcomes 2) PrediXcan analysis of summary statistics 3) 2-sample and multivariate Mendelian randomization analysis to evaluate drug targets. 4) Meta-analysis with MVP and other resources.
Ethical Considerations	None noted
Target Journal	Nature Genetics, Circulation
Milestones *(This section should include the key dates for completion of project, including approval,*	MCS approval: 2-6 weeks Gather COVID outcomes from studies: 2 months Conduct primary genetic association analyses: 2 months

project duration, draft completion, and submission.)	Conduct 2-sample MR and meta-analyses: 2 months Manuscript preparation and co-author review: 2 months