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| **eMERGE Network: Manuscript Concept Sheet** | | |
| **Reference Number**  *(to be assigned by CC)* | NT425NT425 | |
| **Submission Date** | 06/15/2021 | |
| **Project Title** | A multi-ancestry polygenic risk score development and validation for asthma | |
| **Tentative Lead Investigator** *(first author)* | TBD | |
| **Tentative Senior Author**  *(last author)* | Bahram Namjou | |
| **All Other Authors** | Leah Kottyan; Lisa Martin; | |
| **Sites Participating** | Open to all sites  Current participants:  CCHMC | |
| **Background / Significance** | Asthma is the most common chronic condition in children and the third leading cause of hospitalizations in pediatrics. According to GWAS-Catalog, more than 85 GWAS findings have been published with replicable genome wide significance results. However, a polygenic risk score (PRS) with value added across ancestries has not been thoroughly evaluated for this important trait.  Our aim is to develop, train, and validate a PRS relying on genetic determinants for asthma in the context of clinical, environmental, and demographic risk factors to provide useful predictions for disease occurrence in a multi-ancestral cohort.  We used the results from several discovery sets in particular, Trans-National-asthma Genetic Consortium (TAGC; PMID=29273806) and UKbiobank (PMID: 31619474, 29785011) to derive a multi-ethnic PRS score using multiancestral eMERGE cohorts for PRS training and validation. At next step, we will compare the result and will compute and develop the optimum PRS both in pediatrics and adults. These results will enable better disease prediction both in terms of disease onset and asthma severity in conjunction with known clinical risk factors and family history.  **Clinical Implication**: This PRS will be further evaluated to identify children at high risk across a multisite prospective pragmatic trial i.e., a genomic informed risk score for asthma that uses clinical and genetic data to identify individuals at high risk. | |
| **Outline of Project** | We will examine the PRS of asthma using P+T and Bayesian approaches and include covariates (age, sex PCs) into the model in a full trans-ancestry PRS analysis. | |
| **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 (Asthma)  No | |
| **Planned Statistical Analyses** | PRS, logistic regression, ROC and cross validations | |
| **Ethical Considerations** | None | |
| **Target Journal** | Journal of Allergy and Clinical Immunology | |
| **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: 6/2021  Conduct statistical analyses: 6-7/2021  Write manuscript: 7-8/2021  Circulate and submit manuscript: 8-9/2021 | |