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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT386 |
| **Submission Date** | April 8, 2020 |
| **Project Title** | Genetic determinant of primary non-response to Anti-TNF therapy in patients with Inflammatory Bowel Disease |
| **Tentative Lead Investigator** *(first author)* | Tanima De |
| **Tentative Senior Author** *(last author)* | Minoli A. Perera |
| **All Other Authors**  | T. De, H. Zhang, C. Alarcon, B. Lec, J. Avitia, E. Smithberger, Chuyu Chen, M. Horvath, S. Kwan, M. Young, S. Adhikari, J. Kwon, J. Pacheco, eMERGE collaborators, Loukia Parisiadou, Minoli A. Perera |
| **Sites Participating** | Northwestern University and other eMERGE sites  |
| **Background / Significance** | Inflammatory bowel disease (IBD) is a chronic relapsing and remitting disease of the gastrointestinal tract producing debilitating symptoms of diarrhea, abdominal pain and malnutrition. This disorder has two main clinical presentations, Crohn’s Disease (CD) and ulcerative colitis (UC). As with many autoimmune disorders, it is thought that the immune system, genetics, and the environment may all play roles in the predisposition to and severity of IBD. Advances in treatment have led to the development of biologically selective agents targeting tumor necrosis factor alpha (TNFα), a cytokine that plays a central role in the pathogenesis of these disorders. Monoclonal antibody drugs have dramatically improved the ability to treat patients with CD and UC and altered the long-term course and complications of these chronic IBDs. While most patients achieve a clinical response with these agents, approximately 20% of individuals do not respond after initiation of therapy. These individuals are characterized as primary non-responders. Anti-TNFα agents are expensive and are associated with significant risks including serious infections, malignancies, and autoimmune complications. Therefore, the ability to predict which patients would most likely benefit from these biologic therapies is of paramount importance and relevance. We therefore conducted the first GWAS on primary non-response to anti-TNFα agents in IBD and identified a clinically significant variant that can predict patients that are unlikely to respond anti-TNFα agents. We now plan on testing these variants across a wide range of phenotypes by PheWAS using the eMERGE cohort, to determine cross-phenotype associations and clinical relevance, using the ICD diagnosis data that has already been collected across the eMERGE network. |
| **Outline of Project** | The only request for this project from eMERGE is the use of the existing genotype and common variable phenotype data to perform a PheWAS (step iii in outline below), i.e., no new data is being requested.1. Genome-wide genotyping data was obtained on 589 IBD patients and genome-wide association study was performed by logistic regression.
2. The associations were replicated in an independent cohort of 293 patients.
3. The significant variants will be tested across wide range of phenotypes by Phenome-wide Association Study (PheWAS), using the eMERGE PheWAS cohort. Logistic regression will be used for PheWAS association analyses.
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| **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
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| **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):
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| **Does project pertain to an existing eMERGE Phenotype?** | * Yes, if so please list

🗹No |
| **Planned Statistical Analyses** | As described above for steps i & ii completed, & a PheWAS, using logistic regression as stated in outline above. |
| **Ethical Considerations** | This is a retrospective study with no direct interaction with subjects. There will be no loss of confidentiality as the data will be stored in a secured environment and password protected and encrypted computer maintained per NU policy that only the investigators will be able to access. There are no direct benefits to the patients for their participation in this study. However, our research findings may benefit other patients |
| **Target Journal** | Gut |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | Project Approval – April 9-16, 2020Project duration – March 2019 to April 2020Manuscript first draft sent to all co-authors – April 23-30, 2020Co-authors deadline to reply with edits: May 7-14, 2020Final draft of manuscript sent to all co-authors– May 14-21, 2020Manuscript submission to journal- May 21-28, 2020 |

**\*Common Variables available across all datasets:**

* Demographics: sex, year of birth, decade of birth, race, ethnicity
* Codes: (repeated values & age at event): ICD, CPT, Phecodes
* BMI: (repeated value & age at event) height, weight, BMI
* Labs: (lab name, repeated lab value & age at event)
* Medications: (medication name, repeated, & age at event)
* Other: Case/Control status on Phase I and Phase II phenotype: