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| **External Collaborator Proposal** *for* **eMERGE Network Analysis**Project/Manuscript Concept Sheet |
| **Reference Number** | NT284 |
| **Submission Date** | April 30, 2018 |
| **Tentative Lead Investigator** *(first author with contact information and affiliation)* | Marylyn Ritchie, marylyn@pennmedicine.upenn.edu |
| **Tentative Senior Author** *(last author)* | Teri Klein |
| **eMERGE Site Sponsor & Contact** | University of Pennsylvania, Marylyn Ritchie |
| **Project Title** | Validation of PharmCAT annotations |
| **All Other Authors**  | Any interested participants from eMERGE sites |
| **Other eMERGE Sites Involved** | Northwestern, Marshfield, and CCHMC have already confirmed their interest and available clinical annotations for validation. Geisinger has confirmed they do not have clinical annotations for this validation.Any other eMERGE sites included in eMERGE-PGx with clinical annotations to validate are invited to participate.  |
| **Background / Significance** | In a collaboration between the members of the former PGRN-Statistical Analysis Resource (P-STAR), the Pharmacogenomics Knowledgebase (PharmGKB), the Clinical Genome Resource (ClinGen), the electronic Medical Records and Genomics (eMERGE) network, and CPIC, we are developing a software tool to extract PGx variants, beginning with those in published CPIC guidelines, from a genetic dataset resulting from sequencing or genotyping technologies (represented as a .VCF), interpret the variant alleles, infer diplotypes, and generate an interpretation report including CPIC, FDA, or other guideline recommendations. The PharmCAT report can then be used to inform prescribing decisions.  |
| **Outline of Project** | * We are preparing for the beta release of PharmCAT
* Prior to release, we would like to validate PharmCAT annotations with known PGx variant annotations
* Some eMERGE-PGx participants had PGx allele calls validated using a clinical lab for their implementation projects
* We would like to validate PharmCAT annotations by comparing with clinical lab annotations
* This validation experiment would be included as one of the experiments conducted for the PharmCAT software manuscript
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| **Desired Variables** *(essential for analysis**indicated by* ***\*****)* | * age, sex, and race/ethnicity
* allele annotations from clinical lab used by each participating eMERGE site in .csv, .txt, or .json format
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| **Desired Data** | eMERGE-PGx vcf files to annotate select individuals using PharmCAT |
| **Planned Statistical Analyses** | * For any individuals with clinical lab annotations for PGx alleles, we will process their eMERGE-PGx vcf using PharmCAT
* We will compare PharmCAT annotation with annotation from clinical lab
* We will calculate sensitivity and specificity of the PharmCAT annotations
* eMERGE-PGx validation will be included as one of the validation experiments in PharmCAT software manuscript
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| **Ethical Considerations** | None |
| **Available Funding or Resources** | Dr. Ritchie U. Penn funds |
| **Milestones\*\*** | 1. Complete annotations by May 2018
2. Submit PharmCAT software manuscript, which will include eMERGE-PGx validation by end of June, 2018
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***\*\**** *This section should include the timeline for completion of project, including: approval, project duration, first and second draft of the paper and submission.*