**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Submission Date** | 8/17/17 |
| **Reference #** | NT249 |
| **Project Title** | Association between pharmacogenetic polymorphism and urgent care utilization in people with polypharmacy |
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| **All other authors** | Manuel Cabrera, David Fasel, Ning Shang, Shuang Wang, Sinan Zhu, Tatjana Rundek, and interested investigators from other eMERGE sites |
| **Sites Involved** | This study will use data from the eMERGE-III sites. |
| **Background / Significance** | A strong relationship between polypharmacy and negative clinical consequences has been described previously, especially in older adults and people with complex medical conditions. Polypharmacy has been associated with increased health care costs, adverse drug events (ADE), drug-drug interactions, medication nonadherence, impaired functional and cognitive status, falls, urinary incontinence, and malnutrition. Not surprisingly, polypharmacy and potentially inappropriate medication use were shown to be significant contributing factors for frequent hospital admissions and emergency room visits. Recent studies demonstrated that pharmacogenetic polymorphism may play a significant role in facilitating higher urgent care utilization in people with polypharmacy (Finkelstein, 2016; Brixner, 2016). However, a limited number of studies investigated associations between pharmacogenetic polymorphism and urgent care utilization. This study is designed to address this gap in our knowledge. The primary hypothesis to be tested in this study is that adults with polypharmacy and frequent urgent care utilization have a higher frequency of actionable pharmacogenetic polymorphisms as compared to adults with polypharmacy who rarely utilize urgent care. The secondary objective of this study is to conduct deterministic sensitivity analysis using decision trees for assessment of cost-effectiveness of pharmacogenetic testing in adults with polypharmacy.  An enormous burden is imposed on health care because of prescribing inappropriate medication, particularly in the context of adults with polypharmacy and people with complex medical conditions. The overall objective of this project is to explore the potential association between the presence of pharmacogenetic polymorphisms and high urgent care utilization rates in adults with polypharmacy using a nested case–control design. Establishing such an association will support a broader introduction of personalized medicine in the care of adults with polypharmacy and complex medical conditions. |
| **Outline of Project** | In order to assess whether pharmacogenetic polymorphism is an independent risk factor for **f**requent urgent **c**are utilization (FC) in adults with polypharmacy, a nested case–control study will be conducted in adults with polypharmacy with pharmacogenetic polymorphism as an exposure and urgent care utilization as an outcome. The study cohort will comprise adults with 5 or more prescription drugs. The cases will be presented by eligible individuals with the history of FC. The controls will include eligible patients with **i**nfrequent urgent **c**are utilization (IC) randomly drawn from the study cohort, based on case–control matching criteria. On the basis of previous work, cases (FC) are defined as individuals who were hospitalized or attended an emergency room at least 3 times during the past 2 years. The controls will be matched with the cases by age group, gender, race, ethnicity, and chronic disease score (CDS). |
| **Desired**  **Variables (essential for analysis**  **indicated by \*)** | \* Sex/age/race/ethnicity  \* Medication list at the time of genotyping  \* Problem list at the time of genotyping  \* ICD-9 codes for each urgent care event within 5 years  \* Length of stay for each hospitalization  \* ICU indicator during hospital stay  \* SNP genotypes for index pharmacogenes |
| **Desired data** | SNP genotyping data  Smoking history, alcohol or drug use, BMI Creatinine/GFR  Insurance, social and marital status, geocode data |
| **Planned Statistical Analyses** | First, based on identified drug-gene interactions, a binary variable will be constructed representing presence of actionable pharmacogenetic polymorphism. For each subject, total CADD score will be calculated as a sum of CADD scores of individual variants of pharmacogenes found in this subject. Chi-squared test will be used to compare frequency of actionable pharmacogenetics polymorphisms between cases and controls. Mean CADD will be compared in cases and controls using t-test. Stratified analysis based on race, ethnicity and age group will be conducted.    Second, we will perform conditional logistic regression with pharmacogenetic polymorphism or PGx risk score (CADD) as primary independent variable and high urgent care utilization or length of stay as an outcome. Covariates will include medication complexity score, polypharmacy level, GFR, DRG group, insurance type, and socio-economic status (based on geocoding data). Subgroup analysis will be performed in patients with particular chronic conditions and disease severity.  Third, we will conduct deterministic sensitivity analysis using decision trees for assessment of cost-effectiveness of pharmacogenetic testing in adults with polypharmacy. |
| **Ethical considerations** | None anticipated. |
| **Target Journal** | PLoS or JAMA Internal Medicine. |
| **Milestones\*\*** | 9/15/17: Approval of Project  10/1/2017: Clean genetic data sets  10/15/2017: Obtain phenotype data and conduct data analysis  11/15/2017: Finish data analysis, and generate manuscript  12/15/2017: Draft manuscript distributed to co-authors.  01/15/2018: Second draft to co-authors.  02/1/18: Submit manuscript. |

**\*\*** This section should include: Timeline for completion of project, including approval, project duration, first and second draft of the paper and submission.