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Towards Pharmacogenomics-Driven Medication Risk Assessment in People with Polypharmacy

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Abstract. The main objective of this project was to introduce approaches for comprehensive medication risk assessment in people with polypharmacy that simultaneously account for multiple drug and gene effects. To achieve this goal, we developed an integrated knowledge repository of actionable pharmacogenes and a scoring algorithm that was pilot-tested using a data set containing pharmacogenomic information of people with polypharmacy. Metabolic phenotyping using resulting database demonstrated recall of 83.6% and precision of 87.1%. The final scoring algorithm yielded medication risk scores that allowed distinguish frequently hospitalized older adults with polypharmacy and older adults with polypharmacy with low hospitalization rate (average scores respectively: 75.89±15.45 and 10.51±1.82, $p<0.05$). The initial prototype assessment demonstrated feasibility of our approach and identified steps for improving risk scoring algorithms. Pharmacogenomics-driven medication risk assessment in patient with polypharmacy has potential in identifying inadequate drug regimens and preventing adverse drug events.

Keywords. Polypharmacy, pharmacogenomics, decision support

1. Introduction

Polypharmacy has been shown to be a significant risk factor for adverse drug reactions, hospitalization, falls, mortality, and other adverse health outcomes especially in older adults [1]. Previous studies showed high utility of pharmacogenomics for preventing potential side effects of polypharmacy [2]. Pharmacogenomic testing allows identify how hereditary profile affects an individual response to drugs. A recent study has demonstrated that precision medicine has significant potential in people with polypharmacy particularly in older adults with history of urgent care utilization [3].

However, majority of current pharmacogenomic decision support tools doesn't provide assessment of complex drug-drug and drug-drug-gene interactions which are prevalent in people with polypharmacy and may result in adverse drug events or suboptimal drug efficacy. Many of the most frequently prescribed medications for older adults are metabolized by multiple cytochrome pathways, each of which, taken alone,

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insufficiently represents the actual metabolic activity. Thus, development of comprehensive decision support tools accounting for multiple drug interactions is a crucial step in promoting precision medicine in people with polypharmacy.

Our main objective was development of comprehensive pharmacogenomic decision support for medication risk assessment in people with polypharmacy. To achieve this goal, the project addressed two aims: (1) development of comprehensive knowledge repository of actionable pharmacogenes; (2) introduction of scoring approaches reflecting potential adverse effect risk levels of complex medication regimens based on contemporaneous accounting of pharmacogenomic polymorphisms and multiple drug metabolizing pathways.

2. Methods

2.1. Data Source

Information on pharmacogenomic variants and actionable alleles as well as on drug metabolizing pathways is dispersed along various data sources. Based on comprehensive review of literature, the following sources were utilized to build knowledge base for this project: Indiana University Cytochrome P450 (CYP450) Drug Interaction Table, SuperCYP, UpToDate, PharmGKB, and SNPedia. The Indiana University (IU) portal provides a table of major P450 drug interactions and were used as our initial database [4]. SuperCYP contains exhaustive Cytochrome-Drug interaction data [5]. UpToDate is a trusted clinical decision support resource used to retrieve information about substrate weight status for particular drug metabolism pathways [6]. CYP450 enzyme activity for various single nucleotide polymorphisms (SNP), deletions and copy number variations (CNV) were imported from PharmGKB and SNPedia.

2.2. Database

A platform-independent database was created to merge complex data from different data sources. The key component was represented by two tables consisting of drug names and enzyme names. Extended from that, we had detail information saved in individual tables respectively based on contents and source. We had four kinds of detailed tables, each category shared the same schema. The Interactions table contained drug metabolism effects; the IteractionStatus table included effect weight information; the Allele table stored the allele name of the enzymes and the functionality of those allelic variations; and the DrugNames table had the drug aliases such as brand names or chemical names of the drugs that helped normalize drug names coming from different sources.

2.3. Program Structure

Figure 1 represents the structure of Java program that implemented data aggregation and scoring. The application has three working modes: the console mode is used for testing and tracing, which has detailed logs; the UI mode provides a user-friendly interface for quick searches on single patient; The Batch mode will read or write data directly through Excel files. The program is well-documented and provides extensive APIs that allows user to configure the settings and parameters. User can easily create their own scoring

algorithm by overriding methods in Parser class. The program is also guaranteed to be thread safe and have bounded memory usage.

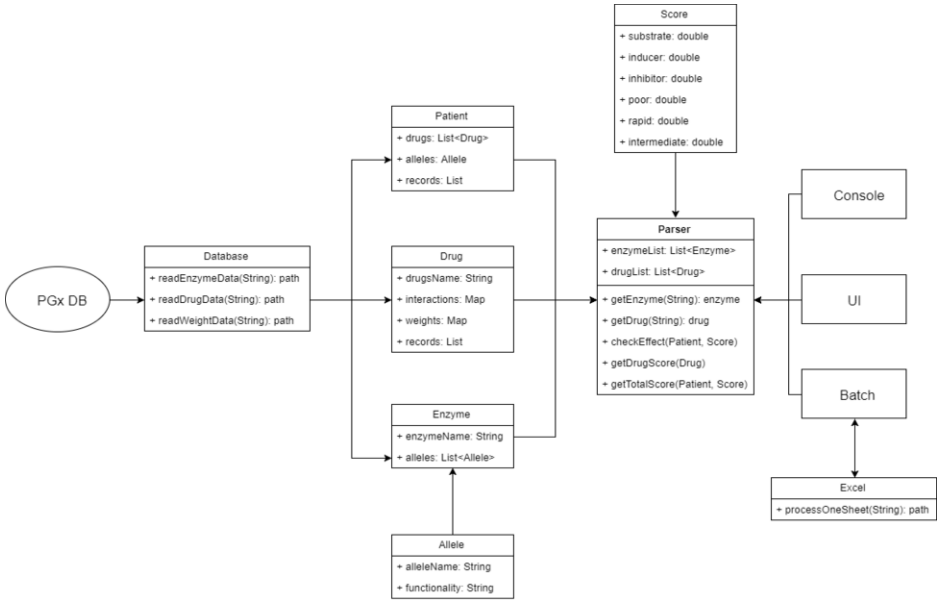

Figure 1. Program structure.

3. Model

In our previous study, we experimented with two algorithms, the additive and multiplicative algorithms, to numerically represent the risk of potential drug interactions based on CYP450 metabolism. We found that the multiplicative approach had limited ability to distinguish two patients' drug-gene interactions [7]. This study represents further development of an additive algorithm.

In additive algorithm, we separated the medication risk assessment score into three parts: drug-drug interaction, drug-gene interaction, and gene function score. The gene function score is used to represent the impact of single nucleotide polymorphisms of CYP450 genes, since allele functionality has a decisive effect on drug metabolism.

Generally, the global medication regimen risk score S is defined as equation 1:

$$S = \sum_{d=1}^{m} |S_d| + \sum_{g=1}^{n} S_g \quad (1) \qquad S_d = \sum_{i=1}^{n} \left(\left(\sum_{j=1}^{m} S_{ji} + S_i \right) * W_i \right) \quad (2)$$

Where S_g is the gene function score, S_d stands for the score for each drug and is a weighted sum of total drug-drug scores and drug-gene score (Equation 2).

In equation 2, i is the binding enzyme of that drug, j is the other drugs the patient also takes and have effects on enzyme i. S_i and S_{ji} represents the drug reaction rate affected by enzyme and other drugs respectively. The weight Wi represents proportion of particular drug metabolism attributed to a specific cytochrome enzyme. The overall scoring framework is illustrated in Figure 2 for an abstract drug Z.

4. Results

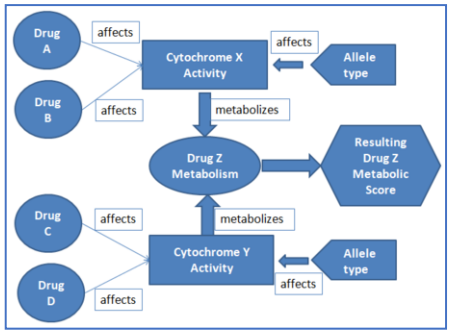

Figure 2. Scoring framework for drug Z.

The resulting database contained information on 956 unique drugs, metabolic phenotypes of 132 alleles within 10 most common cytochromes, 3701 drug-enzyme interaction records reflecting effects of medications on cytochrome activity, and 980 enzyme-drug associations delineating multiple metabolizing pathways of individual drugs. Out of all drug-enzyme interactions, 691 were obtained from IU, 3513 – from SuperCyp, with 503 overlapping relationships, and 67 were imported from legacy pharmacogenomic testing reports (PGx). All enzyme-drug associations were extracted from UpToDate. Out of 132 allele phenotype characteristics, 54 were obtained from SNPedia, 132 – from PharmGKB and 23 from PGx. Validity of the resulting knowledge repository was assessed by comparing drug-enzyme interactions and metabolic phenotypes identified using the resulting database and reports generated by licensed pharmacogenomics laboratories for 31 patients with polypharmacy. The recall ($P(retrieved|relevant)$) and precision $P(relevant|retrieved)$ for drug-enzyme interaction records was 83.58% and 81.16% respectively. For allele metabolic phenotyping, the recall was 84.38%, and precision was 87.10%.

We used twelve patients whose pharmacogenomic profile, medication list and hospitalization records were available for building the scoring system. Among the twelve cases, pharmacogenomic testing indicated actionable genetic polymorphisms in six of them, which affected overall metabolism of their prescribed drugs. These six patients had high hospitalization rate (HHR) than those without significant pharmacogenomics polymorphisms [7]. To obtain optimal parameters for our algorithm, weights for drug-drug interaction, drug-gene interaction and gene function were modeled in series of iterative experiments. Figure 3 shows a graphical view of the patients' average score changes over different factors scaling. We colored the HHR group with red, and low hospitalization rate (LHR) group with blue. The comparison between Figure 3a and Figure 3b indicated that the gene function factor played a key role in distinguishing two groups of patients: the score of HHR group increased rapidly through the increasing of gene function factor. The gene function factor had minor impact on LHR group as expected.

Figure 3c demonstrates the impact of drug-drug interaction and drug-gene interactions in more detail. Since all the test cases have significant polypharmacy, the changes in drug-drug interaction factor lead to obvious change in total score. It also showed that drug-gene interaction factor had more influence in HHR group as well as gene function factor.

The modeling revealed that we should set a higher drug-gene interaction and gene function factors, and keep drug-drug interaction factor as low as possible. In our calculation, the drug-drug interaction factor was eventually set to 0.1 for each competing drug, the drug-gene interaction factor was set to 16, and the gene function factor was 30.

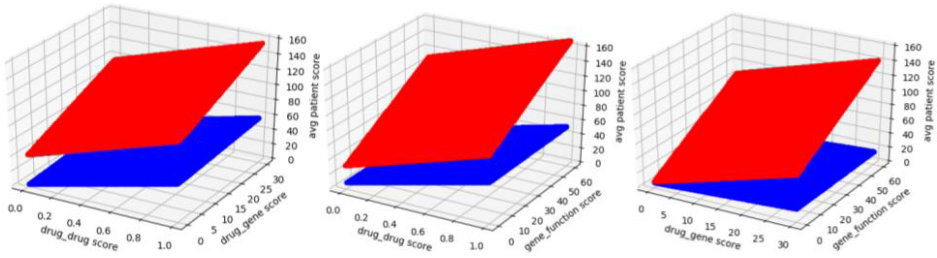

Figure 3. Patient general score over different interaction factors.

We calculated the total score for two groups of patients. Table 1 shows the average percentage of total score components. Depending on the nature of individual polypharmacy and pharmacogenomic profile, there was different contribution of each of three total risk score components. The resulting total risk score for frequently hospitalized older adults with polypharmacy (75.89±15.45) was statistically significantly different ($p<0.05$) from the total risk score for older adults with polypharmacy with low hospitalization rate (10.51±1.82).

Table 1. Average percentage of drug-drug interaction, drug-gene interaction and gene function score in patient's total score

	drug-drug	drug-gene	gene	total score (value)
HHR	0.079	0.325	0.601	75.89±15.45
LHR	0.453	0.549	0.000	10.51±1.82
Total	0.266	0.437	0.300	43.20±12.94

5. Discussion and Conclusion

Our initial goal was to build a prototype of platform-agnostic medication risk scoring system that can potentially help identify patients with polypharmacy in need for optimizing their drug regimens and prioritize pharmacogenomics testing in risk populations with polypharmacy. The initial prototype testing demonstrated feasibility of our approach and helped identify next steps in improving scoring algorithms. Our next step is to utilize larger data sets for training and testing the scoring algorithms.

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