How Common are Drug and Gene Interactions?

Prevalence in a Sample of 1143 Patients with Known CYP Genetics

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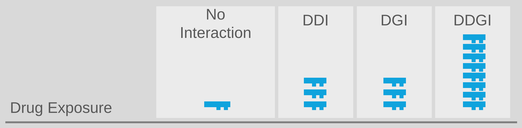
BACKGROUND

- Drug-drug interactions (DDIs) are a major cause of adverse drug reactions. There are two other newly-described important types of interactions: **drug-gene interactions** (DGIs) and **drug-drug-gene interactions** (DDGIs).
- **DGI:** A drug-gene interaction occurs when a patient's genetic metabolic type (for example, CYP2D6 poor metabolizer) affects that patient's ability to clear a drug.
- **DDGI:** In a drug-drug-gene interaction, two patient-specific factors affect that individual's ability to clear a drug: 1) the patient's genetic metabolic type, and 2) another drug in the patient's regimen, such as a potent CYP2D6 inhibitor.

Figure 1. Drug-Drug Interactions, Drug-Gene Interactions, and Drug-Drug-Gene Interactions: The whole Effect Can Be Greater than the Sum of the Parts



- Because actual DDIs are difficult to determine, the literature about DDIs in large samples commonly researches potential DDIs, which are usually identified by using drug interaction software. Potential drug-gene interactions (pDGIs) and potential drug-drug-gene interactions (pDDGIs) can also be identified by reviewing a patient's medication list and genetic test results, with the help of sophisticated software tools.

Figure 2. In a Drug-Drug-Gene Interaction, > 1 of a Drug's Metabolic Pathways May be Inhibited, Increasing Exposure and Increasing the Patient's Risk of Adverse Drug Effects

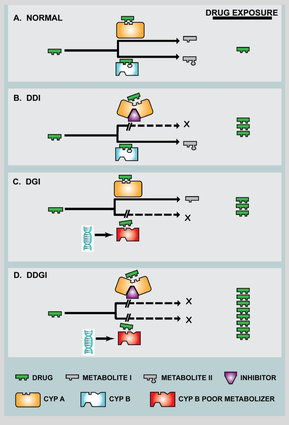


Fig.1A. **Normal**: Expected drug exposure for a substrate that uses two cytochrome (CYP) pathways for metabolism.

Fig. 1B. Drug-drug interaction (**DDI**): Metabolism inhimit in CYPA pathway by an inhibiting co-medication, resulting in an increase to drug exposure.

Fig. 1C. Drug-gene interaction (**DGI**): Metabolism inhibited in CYP 8 pathway by genetics – a "poor metabolzer" pheonotype resulting in an increate to drug exposure.

Fig. 1D. Drug-drug-gene interaction (**DDGI**): Metabolism inhibited in both CYP pathways by an inhibiting co-medication and by genetics – again a "poor metabolizer" phenotype in this example, resulting in an overdose with increased drug exposure

EPIDEMIOLOGY

It is estimated that adverse drug reactions are responsible for about **100,000 deaths yearly**, and are the **4th** to **6th** leading cause of death in the United States[1,2]

Studies of geriatric outpatients have found the percentage of potential DDIs that result in clinically significant adverse drug reactions ranges from **6% to 25%.**[3, 4, 5]

It is likely that drug-gene interactions are common and significant: CYP2D6, CYP2C9, and CYP2C19 are highly polymorphic and are involved in approximately **40% of CYP-mediated drug metabolism**.[6]

OBJECTIVE

This pilot study reports the frequency of potential Drug-Drug Interactions, Drug-Gene Interactions, and Drug-Drug-Gene Interactions in a sample of P450 cytochrome-tested individuals.

METHODS

- The investigators conducted a retrospective analysis of **1143 individuals** whose CYP2D6, CYP2C9, and CYP2C19 genotypes were known. Using each individual's medication list and a software tool called YouScript, the prevalence of potential DDIs, DGIs and DDGIs was calculated.
- The study population included all patients **18 to 89 years of age** who provided a current medication list and submitted a DNA cheek swab sample for CYP polymorphism testing at Genelex Corporation during **2 months** in 2012. Patients across the United States participated.
- **Standard CYP nomenclature was used**: poor metabolizer (PM), intermediate metabolizer (IM), normal metabolizer (NM), rapid metabolizer (RM), and ultra rapid metabolizer (UM).[7, 8]
- The software tool used in the study was designed to analyze cumulative drug-drug and drug-gene interactions based on both data from the literature and a predictive algorithm. By evaluating multiple simultaneous interactions from both drug and gene sources, the software provides a cumulative estimate of pharmacokinetic interactions. In addition, the software alerts users about pharmacodynamic interactions.[9]

The program ranked the severity of each potential interaction using the following definitions:

Table 1: Definitions of Clinical Impact Categories

Clinical Impact	Definition
Major Interaction	• Contraindicated combination • Conditionally contraindicated combination • Significant interactions likely to require action • > 200% increase in AUC predicted • > 90% reduction in AUC predicted
Substantial Interaction	• Interactions that may require monitoring and/or dose adjustments • 75-100% increase in AUC predicted • 60-90% reduction in AUC predicted
Moderate Interaction	• Possible interactions • 25-75% increase in AUC predicted • 25-60% reduction in AUC predicted
No Interaction or Minimal Interaction	• No clinically significant interaction expected • < 25% change in AUC predicted

- The investigators then assigned each interaction a category: **drug-drug interaction, drug-gene interaction**, or **drug-drug-gene interaction**.
- For each patient, the following data was collected: **age**, **number of medications**, and the **number of major or substantial interactions**.

RESULTS

The study population of **1143 patients had a mean age of 60** (range 18 to 89) and patient medication lists contained a mean of **8.4 drugs** (range 1 to 44).

Overall Frequency of Potential Interactions

- **31%** of participants had a potential Drug-Drug Interaction, while **12%** had a potential Drug-Gene Interaction, and **12%** had a potential Drug-Drug-Gene Interaction.

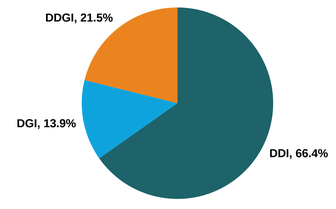
Frequency of Potentially Significant Interactions

- **43%** of participants had potentially significant interactions (categorized as Major or Substantial).
- Potential Drug-Gene Interactions and Drug-Drug-Gene Interactions were quite common in the study population, accounting for **33.9%** of all potentially significant interactions (DDIs, 66.1%; DGIs, 14.7%; DDGIs, 19.2%).
- Most of the potential major interactions were **DDIs (64.6%),** followed by Drug-Drug-Gene Interactions (21.5%), and Drug-Gene Interactions (13.9%); the type distribution was similar for potentially significant interactions (Figure 2).

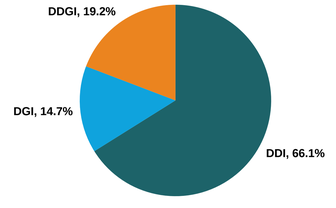
Table 2. Total Number of Potential Significant and Major Interactions

	Potential Substantial or Major Interactions	Potential Major Interactions
Number of Patients	501	321
Number of Interactions	1053	525
Number of Interactions per Patient	2.1	1.6

Figure 2. Distribution of interaction Types in the Study Population
2A. Major Interaction Predicted



2B. Major or Substantial Interaction Predicted
(Potentially Significant Interactions)



Medication Counts

- Patients who had no potential Major or Substantial interactions (56%) had a mean medication count of 6.5, lower than that of the study population [(8.4)].
- Patients with potential Major or Substantial interactions had a mean medication count of 11.0, higher than the mean for the study.

DISCUSSION

- The **frequency** of potential DDIs found in this study (31%) is similar to the percentage observed in Tulner's 2008 study of geriatric patients (37%).[3]
- The study **population** may not be representative of the general US population: patients are often referred for CYP genetic testing because they have already experienced adverse drug effects or medication treatment failures.

CONCLUSIONS

Potential Drug-Gene Interactions and Drug-Drug-Gene Interactions accounted for **33.9%** of all of potential clinically significant interactions identified in this study.

In the study population, potential **Drug-Drug-Gene Interactions were more common** than Drug-Gene Interactions.

When compared to potential DDIs alone, potential Drug-Gene Interactions and Drug-Drug-Gene Interactions increased the number of potential clinically significant interactions by > **50%**.

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In the future, identifying potential Drug-Gene Interactions and Drug-Drug-Gene Interactions may lead to a more comprehensive and effective method for predicting which patients are most likely to experience adverse drug reactions.

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