How common are drug and gene interactions? Prevalence in a sample of 1143 patients with *CYP2C9*, *CYP2C19* and *CYP2D6* genotyping

Aim: Drug–drug interactions (DDIs) are a widely recognized major cause of adverse drug reactions, but two other newly described important types of interactions also exist: drug–gene interactions (DGIs) and drug–drug–gene interactions (DDGIs). A drug–gene interaction occurs when a patient's genetic CYP450 type (e.g., *CYP2D6* poor metabolizer) affects that patient's ability to clear a drug. A drug–drug–gene interaction occurs when the patient's CYP450 genotype and another drug in the patient's regimen (e.g., a CYP2D6 inhibitor) affect that individual's ability to clear a drug. Their prevalence has not been previously described. This pilot study investigates the frequency of DDIs, DGIs and DDGIs in a sample of CYP450 tested individuals. **Materials & methods:** The investigators conducted a retrospective analysis of 1143 individuals with known *CYP2D6*, *CYP2C19* and *CYP2C9* genotypes. Using the individuals' medication lists and YouScript®, a software tool to analyze cumulative DDIs and DGIs, the prevalence of DDI, DGI and DDGIs was analyzed. **Results:** A total of 1053 potential major or substantial interactions were identified in 501 individuals. DDIs accounted for 66.1% of the total interactions. The remaining 33.9% of interactions were DGIs (14.7%) and DDGIs (19.2%). When compared with DDIs alone, DGIs and DDGIs increased the total number of potentially clinically significant interactions by 51.3%. **Conclusion:** In the future, identifying DGIs and DDGIs may lead to a more comprehensive method of identifying individuals who are at risk for adverse drug reactions.

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KEYWORDS: ***CYP2C19*** ▪ ***CYP2C9*** ▪ ***CYP2D6*** ▪ **CYP450** ▪ **cytochrome** ▪ **drug interactions** ▪ **drug–drug** ▪ **drug–gene** ▪ **personalized medicine** ▪ **pharmacogenomics** ▪ **polymorphism**

Paul Verbeurgt*[,1], Tyler Mamiya[1] & Jessica Oesterheld[1]

[1]*Genelex Corporation, 3101 Western Avenue #100, Seattle, WA 98121, USA*
**Author for correspondence:*
Tel.: +1 206 826 1944
Fax: +1 206 219 4000
pharmacist@genelex.com

Adverse drug events, adverse drug reactions & drug–drug interactions

An adverse drug event (ADE) is an injury which results from drug use. An adverse drug reaction (ADR) is a type of ADE that occurs when the drug is noxious, is unintended and occurs at doses normally used in man [1]. According to the FDA and Center for Disease Control and Prevention, ADRs are a major preventable public health problem that cost billions of dollars and affect millions of individuals every year [2,3]. It is estimated that ADRs are responsible for approximately 100,000 deaths yearly and are the fourth to sixth leading cause of death in the USA [4,5].

Drug–drug interactions (DDIs) are a major cause of ADRs, and they can be divided into two categories: pharmacodynamic and pharmacokinetic. Pharmacodynamic interactions occur when one drug modulates another drug's effects in the body. The effects can be additive, antagonistic or synergistic. Pharmacokinetic interactions occur when one drug impacts the absorption, distribution, metabolism or excretion of another drug. This results in increased or decreased concentrations of one or both of the drugs. The CYP450 (CYPs), a family of enzymes responsible for the biotransformation of drugs, are a major cause of pharmacokinetic DDIs [6–9].

DDIs, potential DDIs, prevalence & relationship to ADRs

Most DDI studies are pharmacokinetic studies from small samples. It is very difficult to find and monitor individuals to evaluate actual DDIs in a large population. As a result, most of the literature about DDI prevalence in large samples researches potential DDIs (pDDIs), which are determined by reviewing the medication lists of individuals and finding known interacting drug pairs using either drug interaction computer programs or drug interaction references or data from organizations that monitor drug safety. The prevalence of pDDIs in different clinical samples has been studied [10–13]: depending on the methodology and setting, the prevalence for individuals having a pDDI varies between 6 and 89%. In general, higher percentages of pDDIs are reported for the elderly in in-patient or long-term settings [14,15].

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Not all pDDIs will eventuate in actual DDIs, nor will all DDIs cause clinically significant ADRs [15]. Using a variety of methods for determining ADRs, six studies reported the percentages of pDDIs that resulted in clinically significant ADRs in a variety of inpatient, nursing home and outpatient settings: 0% in elderly inpatients [16]; 6% in elderly outpatients [17]; 15% in elderly outpatients [18]; 25% in elderly outpatients [10]; 50% in elderly nursing home residents [19]; and 70% in inpatients with heart failure [20]. The term DDI will substitute for pDDI in the rest of this paper.

Drug–gene interactions

Genetic testing of CYPs has been available for at least a decade. Three commonly tested CYPs are *CYP2D6*, *CYP2C9* and *CYP2C19*. As a result of CYP testing, two more interactions can now be identified in addition to DDIs: drug–gene interactions (DGIs) and drug–drug–gene interactions (DDGIs).

Although usually not thought of as an interaction, the CYP genotype of an individual can result in very high or low drug concentrations culminating in either toxicity (ADRs) or therapeutic failure when a drug is initiated or added to a drug regimen. We have called this interaction a drug–gene interaction (DGI), a term that has generally been applied to an interaction between a drug and any gene, not just CYP genes [21]. However, the term DGI has recently been employed in this restricted way by researchers from the Center for Drug Evaluation & Research [22], and by other authors [23,24]. It is likely that DGIs are both common and significant since *CYP2D6*, *CYP2C19* and *CYP2C9* are constitutively expressed, highly polymorphic, and are involved in approximately 40% of CYP-mediated drug metabolism [7].

The concept of a DGI is distinct from the concept of phenocopying. Phenocopying is the result of a DDI in which the xenobiotic-metabolizing enzyme phenotype of an individual is changed from their genotype by the administration of another drug. As an example of phenocopying, initiating the potent CYP2D6 inhibitor paroxetine results in changing an individual from the genotype *CYP2D6* extensive metabolizer to the phenotype CYP2D6 poor metabolizer [22].

According to commonly accepted criteria, CYP testing separates individuals with polymorphisms into five categories: poor metabolizers (PMs); intermediate metabolizers (IMs); extensive metabolizers (also termed normal metabolizers [NMs] – the latter term will be used for the rest of the paper); rapid metabolizers (RMs); and ultrarapid metabolizers (UMs) [25,26]. Individuals who are NMs carry two active or one active and one partially active allele, and they respond as expected to drugs when dosed at standard dosing.

Individuals who are PMs have two inactive alleles, and levels of substrate drugs may be increased substantially. PMs may experience increased efficacy and/or increased adverse effects. They may respond to significantly lower doses of medications as compared with NMs. For prodrugs, because the active metabolite is decreased in PMs, individuals may experience a decrease in drug efficacy and also in adverse effects. They may require an increased dose or a change of medication to one that has an alternative metabolic route.

Individuals who are IMs have one active or partially active allele with one inactive allele or two partially active alleles. Levels of substrate drugs may be modestly or moderately increased. Like PMs, these individuals may require decreased dosing of substrate medications. For prodrugs, because the active metabolite is decreased, individuals may require increased dosing or at times, a change of medication to one that uses an alternate metabolic pathway.

Individuals who are RMs have one active and one increased active allele. They are expected to metabolize substrate medications more rapidly and to a greater extent. As a result, active drug levels may be decreased, leading to decreased efficacy and to decreased adverse effects. RMs may require increased dosing of substrate medications. For prodrugs, the active metabolite is increased, which may potentially lead to increased efficacy and to increased adverse effects. RMs may require decreased dosing.

UMs have three or more active alleles or two alleles with increased activity and produce increased levels of enzyme. UMs metabolize substrate medications more rapidly than other individuals. Like RMs, they may require increased doses of substrate medications. For prodrugs, decreased doses of substrate medications or alternative medication may be necessary.

Drug–drug–gene interactions

A drug–drug–gene interaction (DDGI) represents a novel interaction derived from the superimposition of a DDI upon a DGI (Figure 1) [27]. A DDGI can occur when an individual taking a drug metabolized by two CYP pathways is given a medication that inhibits or induces one of the CYP pathways, while their genetics

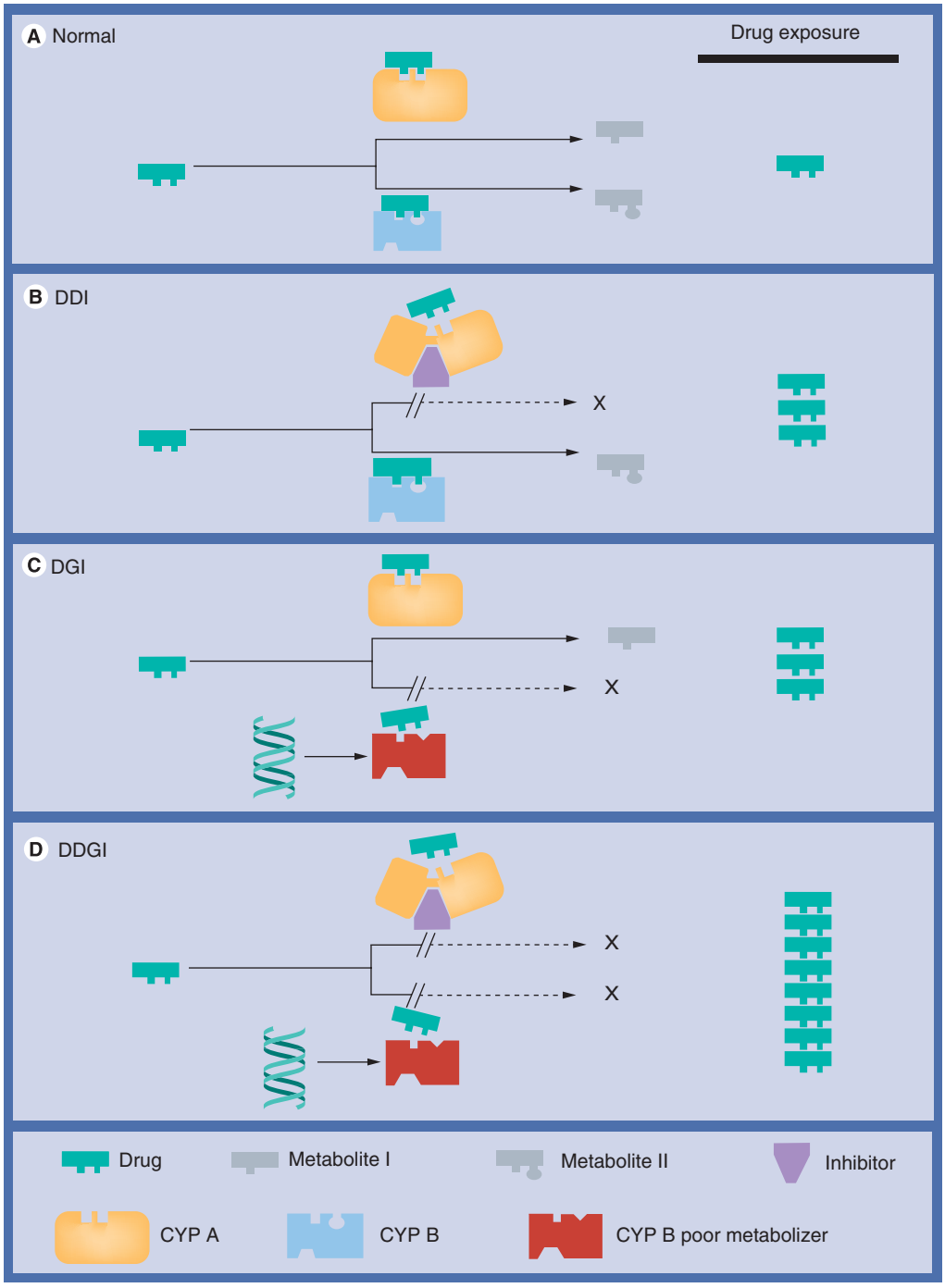

Figure 1. Diagram of how drug–drug, drug–gene and drug–drug–gene interactions impact drug metabolism and exposure. (A) Normal: expected drug exposure for a substrate that uses two CYP pathways for metabolism. **(B)** DDI: metabolism inhibited in the CYP A pathway by an inhibiting comedication, resulting in an increase to drug exposure. **(C)** DGI: metabolism inhibited in the CYP B pathway by genetics – a 'poor metabolizer' phenotype, resulting in an increase to drug exposure. **(D)** DDGI: metabolism inhibited in both CYP pathways by an inhibiting comedication and by genetics – again a 'poor metabolizer' phenotype in this example, resulting in an overdose with increased drug exposure.
CYP: CYP450; DDI: Drug–drug interaction; DDGI: Drug–drug–gene interaction; DGI: Drug–gene interaction.

alters the metabolism of the other pathway(s). The extent of such an interaction will be dependent upon the fraction of the substrate drug that is eliminated via each pathway. An example of this type of interaction is described in a study of individuals taking the antifungal

Table 1. Definitions of clinical impact categories for drug interactions.

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 need monitoring and/or dose adjustments of affected medications 75–200% 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

voriconazole (a CYP3A4 and CYP2C19 substrate) and ritonavir (a potent CYP3A4 inhibitor and potent CYP2C19 inducer). The exposure of voriconazole represented by AUC is increased 26-fold more in *CYP2C19* PMs compared with *CYP2C19* NMs [28]. This large increase in voriconazole AUC is due to the individual's impaired ability to metabolize voriconazole through both CYP2C19 and CYP3A4. Another example of a DDGI is provided by Gschwind *et al.* in patients who are taking acenocoumarol [29]. Individuals who were *CYP2C9* IMs or PMs and who also received CYP2C9 inhibitors had a tripling of the overcoagulation risk compared with individuals who were *CYP2C19* NMs.

Materials & methods

We conducted a retrospective analysis of individuals who had been tested for CYP genetics to determine the prevalence of DDIs, DGIs and DDGIs in the sample. Approval for the study was obtained from the Quorum Institutional Review Board (IRB) (Quorum, WA, USA).

We extracted data from a sample of patients who had submitted specimens to the Genelex Corporation laboratory (WA, USA) to have their CYP polymorphisms identified and who had provided a current medication list. The individual requests were submitted by multiple providers over a course of a 2-month period from across the USA, and they are representative of a heterogeneous US population. Medications included FDA-approved medications, FDA-approved over-the-counter (OTC) drugs, herbal products or supplements. Patients who were less than 18 years of age or more than 89 years of age were excluded.

DNA was extracted from cheek swab samples using a robotic station (QiaGen, MD, USA). Extracted DNA was normalized to 12.5 ng/ml. *CYP2D6* variants were genotyped by xTag v2 *CYP2D6* testing (Luminex Corp., TX, USA). *CYP2C9* and *CYP2C19* variants were genotyped using melt curve PCR genotyping (Roche Molecular Diagnostics, CA, USA) in laboratory-developed multiplex PCR-based assays. These tests accurately identified 16 *CYP2D6* alleles and duplications (active **1*, **2*; inactive **3*, **4*, **5*, **6*, **7*, **8*, **11*, **12*, **14*, **15*; partially active **9*, **10*, **17*, **41*; gene duplications **1*, **2*, **4*, **10*, **41*), nine *CYP2C9* alleles (active **1*, inactive **2*, **3*, **4*, **5*, **6*, **8*, **11*, **13*) and nine *CYP2C19* alleles (active **1*; inactive **2*, **3*, **4*, **5*, **6*, **7*, **8*; rapid **17*) associated with PM, IM, RM or UM status. Phenotypes were classified by their activity in accordance with commonly accepted nomenclature [30]. Genotype calls for *CYP2D6*, *CYP2C9* and *CYP2C19* were achieved in 100% of samples.

Table 2. Drug and gene interaction types.

Type of interaction	Definition
DDI	An interaction solely caused by drug response to a coadministered drug (both pharmacokinetic and pharmacodynamic)
DGI	An interaction solely caused by drug response to CYP450 genetics
DDGI	An interaction that is a cumulative effect of both a DDI and DGI

DDI: Drug–drug interaction; DDGI: Drug–drug–gene interaction; DGI: Drug–gene interaction.

Table 3. Total number of potential significant and major interactions.

	Potentially substantial or major interaction	Potentially major interaction
Number of patients	501	321
Number of interactions (total)	1053	525
Number of interactions per patient	2.1	1.6
Number of DDIs	696 (66.1%)	339 (64.6%)
Number of DGIs	155 (14.7%)	73 (13.9%)
Number of DDGIs	202 (19.2%)	113 (21.5)

DDI: Drug–drug interaction; DDGI: Drug–drug–gene interaction; DGI: Drug–gene interaction.

YouScript®: notes & the algorithm

The core of YouScript®, previously GeneMedRx™, is more than 13,000 paired drug–drug interaction and drug–gene interaction notes that have been abstracted from clinical interaction studies from the literature and from product inserts [30]. Clinical pharmacists have categorized each note as either a pharmacokinetic or pharmacodynamic interaction, or both. If the DDI or DGI is a pharmacokinetic interaction, the pharmacist scores it as to severity into one of four groups based on AUC changes described in the literature: major interaction, substantial interaction, moderate interaction, and minimal or no interaction. When the clinical data is available for drug substrates sensitive to small changes (drugs with a narrow therapeutic range), the pharmacist scores them at a level above their AUC change appropriate to their potential toxicity. Conversely, when there is evidence of little clinical effect despite large AUC changes, the pharmacist scores the interaction down to its clinically appropriate level.

Pharmacists also consider pharmacodynamic interactions. The pharmacodynamic effects of drug combinations may be detrimental, but instances exist where these interactions are beneficial (such as administering probenecid to prolong penicillin half-life). The effects of the drug combination may result in intended drug effects (such as hypotension when combining a β-blocker with a diuretic) or in unintended effects (including increases to potassium when combining ACE inhibitors with trimethoprim). The clinical pharmacist assigns a rating of major interaction, substantial interaction, moderate interaction, and minimal or no interaction to pharmacodynamic interactions, taking into account whether the pharmacodynamic effects are desirable or harmful and the severity of the interaction.

When clinical data is unavailable, the patented algorithm is programmed to predict pharmacokinetic interactions from known metabolic data such as the inhibitory constant (Ki) of the perpetrator drug and the percentage of affected pathway of the victim drug. The pharmacokinetic interactions considered by the algorithm include alterations to absorption, distribution, metabolism and excretion. Metabolism and excretion pathways include phase 1 pathways (including all of the CYP450, esterases and others), phase 2 pathways (including all glucuronidation and

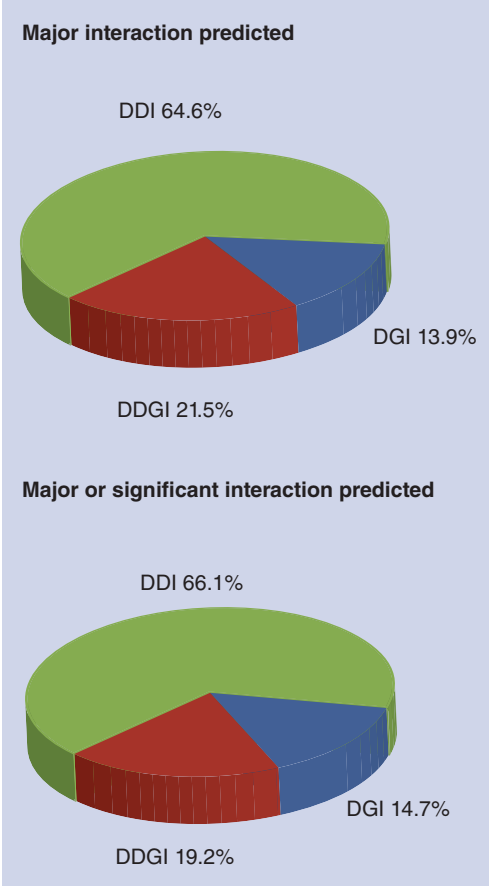

Figure 2. Frequency of drug–drug, drug–gene and drug–drug–gene interactions predicted.
DDI: Drug–drug interaction; DDGI: Drug–drug–gene interaction; DGI: Drug–gene interaction.

Table 4. Top five interacting medications.

Medication	Occurrences (n)	Interactions (%)
Metoprolol	67	12.8
Clopidogrel	53	10.1
Simvastatin	29	5.5
Aspirin	23	4.4
Hydrocodone	23	4.4

sulfation pathways) and ABC and SLC transporters. Both inhibition and induction of drug pairs is taken into account. The algorithm can also predict pharmacokinetic changes based on different genetic phenotypes of *CYP2D6*, *CYP2C9* and *CYP2C19*. The algorithm sums up the effects of all of the pharmacokinetic and pharmacodynamic interactions according to the same four interaction groups as listed above and provides a final rating of the clinical warning (Table 1). A more robust description of the algorithm is available from the registered patent [26,31]. Although the algorithm predicts AUC changes based on CYP genotype and the presence or absence of drugs that are CYP inhibitors or inducers, further complexities, such as exposure to xenobiotics from the environment or the impact of other non-CYP genes that determine drug disposition, are not included. Neither the dose of drug nor the hepatic or kidney function of the individual is taken into account by the algorithm.

Confirmation of drug interactions by pharmacists

YouScript was used to identify all potential interactions. Substantial and major interactions were chosen for analysis based on the assumption that these would be clinically significant. However, the possibility remains that some moderate interactions might also lead to clinically significant outcomes. All predictions of substantial and major interaction generated by YouScript were reviewed by two clinical pharmacists. One pharmacist confirmed each interaction. All predictions were then reviewed by the second pharmacist, and any disagreements were discussed until mutual agreement was formed. YouScript also characterized all interactions as DDIs, DGIs or DDGIs (Table 2).

Age, number of medications, names of medications and number of major or substantial interactions were recorded for each individual. From this data, the prevalence of DDIs, DGIs and DDGIs was calculated.

Table 5. Top five interaction medication classes.

Medication	Occurrences (n)	Interactions (%)
β-adrenergic blocker	82	15.6
Antidepressant	68	13.0
Antiplatelet	53	10.1
Opioid analgesic	52	9.9
Anti-inflammatory	40	7.6

Results

Data from 1190 individuals was analyzed with 47 individuals excluded because of age. Of the remaining 1143 individuals, the ages ranged from 18 years to 89 years with a mean ± SD age of 60 (±15) years. The total number of medications ranged from 1 to 44, with a mean of 8.4 (±5.7) medications and a median of seven medications. Six hundred and forty-two individuals with little potential for interactions (defined as no, or minimal, or moderate interaction according to our categories) had a mean ± SD age of 60 (±14.8) years. The mean medication count for this group was 6.5 (±4.5) with a median of five medications.

We found that 31% (357/1143) of individuals had a DDI, 12% (138/1143) had a DGI and 12% (137/1143) had a DDGI. Individuals with potentially significant interactions (defined as a major or substantial interaction according to our categories) represented nearly half of the dataset (501 individuals or 44% of the total). Some individuals were found to have both a DDI and a DGI or DDGI, and patients averaged a total of 2.1 interactions. The mean age ± SD of individuals with these interactions was 61 (±15) years. The mean medication count ± SD of individuals with a major or significant interaction was 11.0 (±6.0), with a median of ten medications.

We identified 1053 major or substantial interactions in the 501 individuals with potentially significant interactions. Each patient had on average 2.1 major or substantial interactions. The results are summarized in Table 3 based on type of interaction. DGIs represented 14.7% of all interactions and DDGIs represented 19.2% for a total of 33.9% of all interactions. The remaining interactions (66.1%) were DDIs.

When limited only to the patients with major interactions, the relative representation of the three types of interactions, DDI, DGI and DDGI, is similar to major and substantial interactions. When considering only major interactions, DGIs represent 13.9% of all interactions, and DDGIs represented 21.5% of all interactions – a total of 35.4% of all interactions.

Table 6. Allele frequency for *CYP2D6*, *CYP2C19* and *CYP2C9*.

CYP2D6		*CYP2C19*		*CYP2C9*	
Allele	***n (%)***	***Allele***	***n (%)***	***Allele***	***n (%)***
**1*	952 (41.8)	**1*	1490 (65.3)	**1*	1873 (82.2)
**2*	86 (3.8)	**2*	340 (14.9)	**2*	235 (10.3)
**2A*	438 (19.2)	**3*	3 (0.1)	**3*	139 (6.1)
**3*	31 (1.4)	**4*	5 (0.2)	**5*	5 (0.2)
**4*	354 (15.6)	**6*	1 (0.0)	**6*	1 (0.0)
**5*	76 (3.3)	**8*	7 (0.3)	**8*	14 (0.6)
**6*	20 (0.9)	**17*	436 (19.1)	**11*	9 (0.4)
**8*	1 (0.0)			Unknown†	2 (0.1)
**9*	56 (2.5)				
**10*	58 (2.5)				
**17*	49 (2.2)				
**41*	153 (6.7)				
Unknown†	2 (0.1)				
Duplications	66 (2.8)‡				
Grand total	2276 (100.0)		2282 (100.0)		2278 (100.0)

†The combination of variants were unusual and an allele designation was not available at analysis.
‡Percentage for duplications based on number of patients and not number of alleles. Duplications not counted towards allele grand total.

The remaining interactions (64.6%) were DDIs. Figure 2 displays the interactions by interaction category. Adding the DGI and DDGI interactions together yields the total number of interactions associated with genetic polymorphisms. This represents a 51.3% increase (1053 vs 696) of major or substantial interactions above the prevalence of DDIs alone. When considering major interactions only, there is a 54.9% (525 vs 339) increase of genetic interactions above DDIs.

Medications most frequently involved in major interactions were metoprolol, clopidogrel, simvastatin, aspirin and hydrocodone. These medications included both victim and perpetrators and were involved in either pharmacokinetic or pharmacodynamic interactions. The most common medication classes causing major interactions include β-adrenergic blocking agents, antidepressants, antiplatelets, opioid analgesics and anti-inflammatory agents (Table 4 & 5).

Discussion

The major finding of this study is that, in a sample of individuals who have had CYP testing, DGIs and DDGIs represent a significant percentage of the total interactions. DGIs and DDGIs accounted for 33.9% of the total

Table 7. Phenotype frequency for *CYP2D6*, *CYP2C19* and *CYP2C9*.

CYP2D6		*CYP2C19*		*CYP2C9*	
Phenotype	***n (%)***	***Phenotype***	***n (%)***	***Phenotype***	***n (%)***
Extensive metabolizer	634 (55.6)	Extensive metabolizer	494 (43.3)	Extensive metabolizer	780 (68.5)
Intermediate metabolizer†	405 (35.5)	Intermediate metabolizer	302 (26.5)	Intermediate metabolizer	315 (27.7)
Poor metabolizer	52 (4.6)	Poor metabolizer	27 (2.4)	Poor metabolizer	44 (3.9)
Ultrarapid metabolizer‡	49 (4.3)	Rapid metabolizer	267 (23.4)		
		Ultrarapid metabolizer	51 (4.5)		
Grand allele total	1140		1141		1139

†Twelve individuals' CYP2D6 phenotypes had two possible phenotypes: CYP2D6 intermediate metabolizer or CYP2D6 extensive metabolizer. In these scenarios, the individual was classified as the worst-case scenario phenotype, CYP2D6 intermediate metabolizer.
‡Nine individuals' CYP2D6 phenotypes had two possible phenotypes: CYP2D6 ultrarapid metabolizer or CYP2D6 extensive metabolizer. In these scenarios, the individual was classified as the worst-case scenario phenotype, CYP2D6 ultrarapid metabolizer.

Table 8. Individuals with one or more variation in each particular CYP450.

	Current study	Villagra *et al.* [33]
No variations	67 (5.9%)	7.4%
CYP2D6	214 (18.7%)	32.9%
CYP2C19	107 (9.4%)	4.9%
CYP2C9	36 (3.1%)	3.2%
Subtotal (variations in one CYP)	357 (31.2%)	41.0%
2D6+2C19	394 (34.5%)	25.2%
2D6+2C9	180 (15.7%)	19.1%
2C19+2C9	31 (2.7%)	0.7%
Subtotal (variations in two CYPs)	605 (52.9%)	45.0%
2D6+2C9+2C19	114 (10.0%)	6.6%
Total	1143 (100.0%)	100.0%

Variations were considered any allele detected other than each *1 *for each* CYP *and* *2 *for* CYP2D6 *per Villagra* et al. [33] *study design.*

of potential clinically significant interactions, which increased the number of potential clinically significant interactions by 51.3% when compared with those generated by DDIs alone. We also determined that the number of DDGIs (19.2% of all interactions) was greater than DGIs (14.7%).

Comparison to other outpatient samples

Our sample came from multiple providers across the USA. From anecdotal information from providers, the most common reasons for providers to submit samples for CYP testing is because of significant adverse effects or medication treatment failures experienced by patients. Similar indications for CYP testing were seen in a study with 1199 psychiatry outpatients [32]. Because of this selection bias, the study prevalence of DDIs, DGIs and DDGIs is best applied to CYP-tested samples.

The most similar samples to compare results of this study are those from the clinical DDI literature that focuses only on DDI prevalence rather than on DGI and DDGI prevalence. In our sample, 31% of individuals had a DDI, which is similar to the Tulner study of geriatric outpatients, wherein 37% (300/807) of individuals had a DDI [10]. As expected, since the percentage of individuals with DDIs is increased in elderly individuals in in-patient and long-term facilities, our finding of 31% is appropriately less than the 80% of individuals with DDIs in a geriatric inpatient sample determined by a CYP450-DDI computer software, InterMED-Rx [33].

Our sample had a mean (SD) age of 60 (±15) years and received a mean (SD) of 8.4 (±5.7) medications, OTCs, herbals and supplements. The mean (SD) number of medicines is slightly higher than in other studies of outpatients: 5.1 (±3.6) drugs in Tulner's 2008 European study [10], 6.8 (±3.3) in an elderly European study [34], 5.8 (±2.4) in a Taiwanese study [35] or the six prescriptions and OTC medications in a community-dwelling adult study in the USA [36]. This number is less than the 12.2 medications found in a sample of hospitalized elderly (mean age 82.3 years) in Zakrzewski-Jakubiak's 2011 study [33]. An exact comparison of the mean number of medications may not be possible because herbals, supplements and OTCs may have been excluded or not reported in all studies.

A comparison of the CYP frequencies in our sample to those in a study reporting the frequencies of *CYP2C9*, *CYP2D6* and *CYP2C19* in 1199 psychiatry outpatients in the USA shows that in this study, 62.9% of patients had variants in two or three CYPs, compared with 51.6% in the Villagra study [32] (see Tables 6–8). In our sample, 5.9% of individuals were not polymorphic in any of the three CYPs, 31.2% had variations in one CYP, 52.9% of individuals had variants in two CYPs and 10.0% had variations in all three CYPs tested, compared with the results of individuals in the Villagra *et al.* study of 7.4% not polymorphic in any of the CYPs, 41.0% for variations in one CYP and 25.0% for variations in two CYPs and 6.6% in all three CYPs. A plausible explanation for the increased variance is that our sample is laboratory-tested for more allelic variants than the sample from the laboratory in the Villagra study [32].

In summary, the number of DDIs and the CYP polymorphisms are similar in this study to other outpatient DDI samples, but it appears that the mean number of medications used by individuals in this CYP-tested sample may be slightly higher than in other outpatient samples. Our sample may have contained a more accurate list of medications, or individuals with an increased number of medications are more likely to be referred for CYP testing. It remains to be determined if either explanation is confirmed by other CYP-tested populations when evaluated in the future for DDIs, DGIs and DDGIs.

The most common drugs involved in DDIs depends both on the country in which the study occurred (e.g., digitalis in Germany or potassium chloride in Denmark), as well as the medical setting in which the study was investigated (e.g., midazolam and fentanyl in an ICU setting

or lithium in an outpatient psychiatric setting) [15,37]. No prevalence data exists for the most common drugs implicated in DGIs or DDGIs. Further studies on CYP-tested outpatients may confirm whether the drugs found in this study (e.g., metoprolol, clopidogrel, simvastatin, aspirin and hydrocodone) are the most common medications involved in interactions.

Limitations of the study

The prevalence of DDIs is likely close to a true value, since YouScript takes account of the composite outcome of literature-based and algorithm-calculated DDIs of phase 1 metabolic pathways (including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4/5); phase 2 pathways (including glucuronidation, sulfation and others) and ABC and SLC transporters. Pharmacodynamic DDIs, duplicative adverse effects and DDIs of absorption are also considered. However, because drug dosage and liver and kidney function are not taken into account, the severity of the interactions may not be accurate, and therefore represents a limitation of the study.

The prevalence of DGIs and DDGIs was based on the three most commonly tested genetic variations, *CYP2C9*, *CYP2D6* and *CYP2C19*. The true prevalence of DGIs and DDGIs may be an underestimation if one considers the possible metabolic genetic variations that were not evaluated, including other CYP enzymes (CYP1A2, CYP2B6, CYP3A4), phase 2 metabolic pathways and transporters. As genetic testing of these pathways becomes more common, the prevalence of DGIs and DDGIs is expected to increase.

Finally, in this study, the prevalence of DDIs, DGIs and DDGIs measure only potentially significant clinical interactions. An ideal study would also determine if an actual interaction occurred and would assess efficacy and toxicity. In the meantime, it is hoped that other studies of CYP-tested populations will be undertaken to assess if the results of this pilot study are representative of other samples. Other topics for further study of CYP-tested populations could include the evaluation of the prevalence of DDIs, DGIs and DDGIs for each specific tested CYP, the evaluation of whether the frequency of these subtypes of interactions correlates with increasing age, and an examination of the most common drugs that are associated with each subtype.

Conclusion

Our pilot study supports the idea that previous ADR predictions based solely on DDIs may be missing a large proportion of potential clinically significant interactions. With the advent of genetic testing and sophisticated computer-based algorithms, it is now possible to include DGIs and DDGIs with DDIs, which our study indicates may make up more than a third of all potential clinically significant interactions. Further testing may elucidate the scope of potentially undetected ADRs. Follow up studies are recommended.

Future perspective

Adverse drug reactions contribute to the morbidity and mortality of patients and may cost American healthcare billions of dollars each year. In the pre-CYP testing era, investigators determined DDIs by finding pairs of known interacting drugs; however, since the advent of genetic testing and sophisticated computer programs, it may now be possible to improve interaction predictions and identify additional causes contributing to ADRs. It is important that future studies examine pharmacogenetics as well as drug absorption, distribution, metabolism and elimination in order to improve the public knowledge, scope and predictive ability of personalized medicine.

Executive summary

Background

- Adverse drug reactions (ADRs) are a major preventable public health problem. Better identification of ADRs can save money and lives.
- Drug–drug interactions (DDIs) are recognized as a major cause of ADRs. However, in addition to DDIs, CYP genotyping now allows drug–gene interactions (DGIs) and drug–drug–gene interactions (DDGIs) to be identified as a potential source of ADRs as well.

Results

- 1053 major or substantial interactions in 501 individuals.
- DGIs represented 14.7%, DDGIs 19.2% and DDIs 66.1% of major or substantial interactions.
- DGIs represented 13.9%, DDGIs 21.5% and DDIs 64.6% of major interactions.

Conclusion

- Identification of DGIs and DDGIs increased the number of potential clinically significant interactions by approximately 50% as compared with DDIs alone.
- This increased the number of individuals identified with potential clinically significant ADRs.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

1 WHO. International drug monitoring: the role of national centres. Report of a WHO meeting. *World Health Organ. Tech. Rep. Ser.* 498, 1–25 (1972).

2 FDA. Safe use initiative: collaborating to reduce preventable harm from medications (2009). www.fda.gov/downloads/drugs/drugsafety/ucm188961.pdf

3 Centers for Disease Control and Prevention: Medication Safety Programme (2010). www.cdc.gov/medicationsafety/basics.html

4 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 279(15), 1200–1205 (1998).

5 Giacomini KM, Krauss RM, Roden DM, Eichelbaum M, Hayden MR, Nakamura Y. When good drugs go bad. *Nature* 446(7139), 975–977 (2007).

6 Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA* 286(18), 2270–2279 (2001).

7 Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. *Trends Pharmacol. Sci.* 25(4), 193–200 (2004).

8 Hisaka A, Ohno Y, Yamamoto T, Suzuki H. Prediction of pharmacokinetic drug–drug interaction caused by changes in cytochrome P450 activity using *in vivo* information. *Pharmacol. Ther.* 125(2), 230–248 (2010).

9 Sanchez Munoz-Torrero JF, Barquilla P, Velasco R *et al.* Adverse drug reactions in internal medicine units and associated risk factors. *Eur. J. Clin. Pharmacol.* 66(12), 1257–1264 (2010).

10 Tulner LR, Frankfort SV, Gijsen GJ, Van Campen JP, Koks CH, Beijnen JH. Drug–drug interactions in a geriatric outpatient cohort: prevalence and relevance. *Drugs Aging* 25(4), 343–355 (2008).

11 Marzolini C, Elzi L, Gibbons S *et al.* Prevalence of comedications and effect of potential drug–drug interactions in the Swiss HIV Cohort study. *Antivir. Ther.* 15(3), 413–423 (2010).

12 Smithburger PL, Kane-Gill SL, Seybert AL. Drug–drug interactions in cardiac and cardiothoracic intensive care units: an analysis of patients in an academic medical centre in the US. *Drug Saf.* 33(10), 879–888 (2010).

13 Mino-Leon D, Galvan-Plata ME, Doubova SV, Flores-Hernandez S, Reyes-Morales H. A pharmacoepidemiological study of potential drug interactions and their determinant factors in hospitalized patients. *Rev. Invest. Clin.* 63(2), 170–178 (2011).

14 Lamy PP. The elderly and drug interactions. *J. Am. Geriatr. Soc.* 34(8), 586–592 (1986).

15 Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug–drug interactions. *Expert Opin. Drug Saf.* 11(1), 83–94 (2012).

16 Glintborg B, Andersen S, Dalhoff K. Drug–drug interactions among recently hospitalised patients – frequent but mostly clinically insignificant. *Eur. J. Clin. Pharmacol.* 61(9), 675–681 (2005).

17 Obreli-Neto PR, Nobili A, De Oliveira Baldoni A *et al.* Adverse drug reactions caused by drug–drug interactions in elderly outpatients: a prospective cohort study. *Eur. J. Clin. Pharmacol.* 68(12), 1667–1676 (2012).

18 Kurfees JF, Dotson RL. Drug interactions in the elderly. *J. Fam. Pract.* 25(5), 477–488 (1987).

19 Tamai I, Strome L, Marshall C, Mooradian A. Analysis of drug–drug interactions among nursing home residents. *Am. J. Hosp. Pharm.* 46(8), 1567–1569 (1989).

20 Kohler GI, Bode-Boger SM, Busse R, Hoopmann M, Welte T, Boger RH. Drug–drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. *Int. J. Clin. Pharmacol. Ther.* 38(11), 504–513 (2000).

21 Karczewski KJ, Daneshjou R, Altman RB. *Chapter 7: Pharmacogenomics*. In: *PLoS Comput. Biol.* Lewitter F, Kann M (Eds) (2012).

22 Conrado DJ, Rogers HL, Zineh I, Pacanowski MA. Consistency of drug–drug and gene–drug interaction information in US FDA-approved drug labels. *Pharmacogenomics* 14(2), 215–223 (2013).

23 Peterson JF, Bowton E, Field JR *et al.* Electronic health record design and implementation for pharmacogenomics: a local perspective. *Genet. Med. Official J. Am. Coll. Med. Genet.* 15(10), 833–841 (2013).

24 Tod M, Nkoud-Mongo C, Gueyffier F. Impact of genetic polymorphism on drug–drug interactions mediated by cytochromes: a general approach. *AAPS J.* 15(4), 1242–1252 (2013).

25 Kubica A, Kozinski M, Grzesk G, Fabiszak T, Navarese E, Goch A. Genetic determinants of platelet response to clopidogrel. *J. Thromb. Thrombolysis* 32(4), 459–466 (2011).

26 Bjorkman IK, Fastbom J, Schmidt IK, Bernsten CB. Pharmaceutical care of the elderly in europe research G: drug–drug interactions in the elderly. *Ann. Pharmacother.* 36(11), 1675–1681 (2002).

27 Kisor DF, Munro C, Loudermilk E. Pharmacogenomics and the most commonly prescribed drugs of 2011. *Pharm. Times* (2012).

www.pharmacytimes.com/publications/issue/2012/December2012/Pharmacogenomics-and-the-Most-Commonly-Prescribed-Drugs-of-2011

28 Mikus G, Schowel V, Drzewinska M *et al.* Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. *Clin. Pharmacol. Ther.* 80(2), 126–135 (2006).

29 Gschwind L, Rollason V, Boehlen F *et al.* Impact of CYP2C9 polymorphisms on the vulnerability to pharmacokinetic drug–drug interactions during acenocoumarol treatment. *Pharmacogenomics* 14(7), 745–753 (2013).

30 Sim SC. The human cytochrome P450 (CYP) allele nomenclature database (2013). www.cypalleles.ki.se

31 Patterson R, Oesterheld JO. Genetic data analysis and database tools. US Patent #US8311851 (2012). www.google.com/patents/US8311851

32 Patterson R, Oesterheld JO. Genetic data analysis and database tools. US patent #US8099298 (2012). www.google.com/patents/US8311851

33 Villagra D, Goethe J, Schwartz HI *et al.* Novel drug metabolism indices for pharmacogenetic functional status based on combinatory genotyping of *CYP2C9*, *CYP2C19* and *CYP2D6* genes. *Biomarkers* 5(4), 427–438 (2011).

34 Zakrzewski-Jakubiak H, Doan J, Lamoureux P, Singh D, Turgeon J, Tannenbaum C. Detection and prevention of drug–drug interactions in the hospitalized elderly: utility of new cytochrome P450–based software. *Am. J. Geriatr. Pharmacother.* 9(6), 461–470 (2011).

35 Hoffmann W, Van Den Berg N, Thyrian JR, Fiss T. Frequency and determinants of potential drug–drug interactions in an elderly population receiving regular home visits by GPs–results of the home medication review in the AGnES-studies. *Pharmacoepidemiol. Drug Saf.* 20(12), 1311–1318 (2011).

36 Lin CF, Wang CY, Bai CH. Polypharmacy, aging and potential drug–drug interactions in outpatients in Taiwan: a retrospective computerized screening study. *Drugs Aging* 28(3), 219–225 (2011).

37 Heuberger R. Polypharmacy and food–drug interactions among older persons: a review. *J. Nutr. Gerontol. Geriatr.* 31(4), 325–403 (2012).