Cytochrome P-450 gene and drug interaction analysis in patients referred for pharmacogenetic testing

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Purpose. The results of a study of variant cytochrome P-450 (CYP) alleles and associated risks of drug–drug interactions (DDIs) and altered drug metabolism are reported.

Methods. The records of a pharmacogenetic testing laboratory were retrospectively analyzed to identify patients tested for polymorphisms of genes coding for five CYP isozymes important in drug metabolism (CYP2D6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5) over a 16-month period. Based on the results of phenotyping, the patients were categorized by expected CYP isozyme activity (e.g., normal or poor metabolizer, expresser or nonexpresser). Using proprietary Web-based software, researchers analyzed phenotyping data and medication lists submitted by patients to determine the potential for DDIs, drug–gene interactions (DGIs), and drug–drug–gene interactions (DDGIs).

Results. In the mixed-race study population of more than 22,000 male and female patients (age range, 1–108 years; mean, 60 years), phenotypes associated with alterations of CYP metabolic pathways were common. Among patients in whom phenotypes for all five isozymes of interest were determined (n = 14,578), about 93% were not categorized as normal metabolizers of all five proteins. In many cases, potential interaction threats were rated by clinicians as severe enough to warrant implementation or consideration of a medication regimen change or dose adjustment. Analysis of patient-provided medication lists indicated frequent use of medications posing DDI, DGI, or DDGI risks.

Conclusion. In a mixed-race population of over 20,000 U.S. patients, CYP gene polymorphisms associated with DDIs and other interaction threats were prevalent, and most individuals were not categorized as normal metabolizers of all five CYP isozymes of interest.

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The important role that genetics plays in medication response (both positive and negative) is well accepted. For some individual medications, there is a clear advantage in genetic testing as a means of improving patient outcomes. One example is testing to determine the presence of a loss-of-function allele of *CYP2C19*, the gene coding for cytochrome P-450 (CYP) isozyme 2C19, prior to the use of clopidogrel in order to prevent stent thrombosis in patients undergoing percutaneous coronary intervention (PCI) with stent placement. Meta-analyses have found an increased risk of stent thrombosis or other major adverse cardiovascular events in post-PCI patients who are carriers of a *CYP2C19* loss-of-function allele.[1,2] Having an understanding of this potentially life-threatening issue prior to use of a medication has obvious clinical implications. In this example, the Food and Drug Association (FDA) has issued a black-box warning for clopidogrel, advising healthcare professionals to consider using an alternative antiplatelet medication in patients identified as CYP2C19 poor metabolizers.[3]

The role of routine genetic testing focused on the most significant CYP isozymes (CYP2D6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5) is less clearly defined.[4] Understanding the metabolic profile of a patient

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allows the provider to identify drug–gene interactions (DGIs) and drug–drug–gene interactions (DDGIs), thus facilitating adjustments in the medication regimen and avoiding potential lack of effectiveness or adverse drug reactions. A DGI is a type of interaction involving a drug and a gene coding for a CYP isozyme or other protein.[5] In a study published in 2014, it was reported that while drug–drug interactions (DDIs) accounted for 66.1% of interactions in a population of 501 patients, DGIs accounted for 14.7% of all potential major and substantial interactions identified.[6] A DDGI involves a complex interaction that results from the superimposition of a DDI on a DGI. In the above-mentioned study, DDGIs accounted for 19.2% of all potentially major and substantial interactions.[6]

We performed a retrospective analysis of data on over 20,000 patients who were referred for pharmacogenetic testing and drug interaction screening with YouScript (Genelex Corporation, Seattle, WA), an evidenced-based clinical decision support tool that identifies DDIs, DGIs, and DDGIs. For this study, we focused on drug interactions that involve CYP metabolic pathways. Specifically, we examined the frequency of metabolic CYP phenotypes, the most common interacting medications, the severity of interactions by interaction type, and differences in interaction severity between younger and older patients. The results of the study are presented here, followed by a discussion of the potential implications associated with routine genetic testing and the results of an interaction analysis of the population at large and a "high-risk" subpopulation.

KEY POINTS

- When considering the CYP isozymes responsible for the majority of drug metabolism, most individuals are not normal metabolizers.
- Nearly half of the most severe potential interactions are in part due to genetically determined variations in drug metabolism.
- The population of individuals 65 years of age or older is the most susceptible to severe potential interactions and may benefit the most from routine CYP gene–focused testing.

Methods

Population selection and patient data collection. This retrospective analysis was approved by the Quorum Review IRB, an independent ethics review board. Patients who agreed to undergo testing and also consented to the use of their deidentified data for research purposes were included in this analysis. All consenting patients referred to Genelex for pharmacogenetic testing (outside of clinical trials) from May 12, 2013, through September 30, 2014, were included. The following data were collected in a secure database for deidentified population-level review:

- Patient ZIP code, date of birth, sex, race or ethnicity (when available); date of specimen collection; referring provider (typically a physician or nurse practitioner but in some cases a pharmacist), when allowed by individual states; referring provider specialty (when available); diagnosis codes for testing; and a medication list, and
- Data determined by CYP-focused gene testing and interaction analysis and subsequently reported to the provider, including reporting date, phenotypes (for the genes tested), genotypes (for the genes tested), interaction type (DDI, DGI, or DDGI), "victim" drug (the drug affected by the interaction), causative drug or gene (the "perpetrator" of the interaction), and clinician-rated severity level for each interaction (Table 1).

The above-listed information was evaluated across the entire population and also analyzed via subgroup analysis of a high-risk group of patients who were 65 years of age or older at the time of testing. Data on all patients who underwent testing focused on one or more of five specified CYP isozyme–encoding genes (*CYP2D6, CYP2C9, CYP2C19, CYP3A4,* and *CYP3A5*) were included in the analysis.

Genetic testing and phenotype determination. Testing was carried out by Genelex, which is accredited by the College of American Pathologists (CAP 1073709) and licensed to perform high-complexity clinical testing in all U.S. states. Genotypes

Table 1. Categories for Clinician Rating of Interaction Severity

Category	Description/Recommendation
Change	Highest-risk interaction; reserved for interactions that should be avoided in almost all scenarios. Recommendation to change one or more current medications based on contraindications and/or documented clinical literature.
Consider	Recommendation to consider changing the medication regimen or adjusting the dose of one or more current medications based on documented clinical literature and/or known pharmacokinetic properties.
Monitor	Monitor closely for drug-specific decreased effectiveness and/or adverse effects, as the patient may be at increased risk.
No change	No changes in medication regimen or dose adjustments are warranted.

were obtained using a laboratory-developed multiplex polymerase chain reaction–based test followed by a single base primer extension assay for variant detection by the MassARRAY system (Agnea Biosciences, San Diego, CA). The variants tested for included the following (listed by gene and allele designation[s]): *CYP2C19*2–*10, *12,* and **17*; *CYP2D6*2, *2A, *3–*12, *14A, *15, *17, *19, *20, *29, *36,* and **41* (and gene duplications); *CYP2C9*2–*6, *8, *11, *13,* and **15*; *CYP3A4*22*; and *CYP3A5*3*. The absence of a positive test result for all variants listed resulted in classification of the genotype as wild type (unmutated).

Phenotypes were classified according to the expected enzyme activity associated with the combination of alleles detected. For example, *CYP2D6* phenotypes were categorized as resulting in normal, intermediate, poor, or ultrarapid CYP2D6 metabolism. In situations wherein a definitive phenotype could not be assigned—for example, cases involving rare unpublished haplotypes or *CYP2D6* duplications whose affects on drug metabolism and interaction risk were uncertain—the phenotype was excluded from the frequency analysis; however, in these situations, interactions were reported according to the worst-case scenario. Based on the results of phenotyping, patients were (as applicable) categorized as normal, intermediate, or poor *CYP2C9* metabolizers; as normal, intermediate, poor, or ultrarapid *CYP2C19* metabolizers; and as normal or intermediate *CYP3A4* metabolizers. Patients who underwent *CYP3A5* phenotyping were categorized as nonexpressers, intermediate expressers, or expressers. Nonexpressers have greatly decreased CYP3A5 isozyme activity; however, theirs is the most common phenotype, and standard dosing is generally recommended for them.

Evaluation of data. Blood or buccal genetic samples were accompanied by a list of the patient's current medications. On completion of the patient's genetic testing, the phenotype and medication list were entered into the Web-based YouScript software.[7-12] Potential interactions were interpreted by clinicians employed by Genelex, including pharmacists and a physician who issued a report with management recommendations (discussed below). Referring providers always received the patient's results as a report. If a medication list was submitted, the report contained the clinician-issued management recommendations. If no medication list was submitted, a report was issued with the genotype and phenotype information only. The referring provider also had access to the patient's profile in the YouScript system, which was prepopulated with data on the patient's submitted medications and CYP phenotype status.

Drug and gene interaction software. The software used in the study is an evidenced-based clinical decision support tool that identifies DDI, DGI, and DDGI risks.[7-12] It has been previously described by Verbeurgt et al.[6] Drug interaction information obtained from the program was summarized and presented to the referring provider in order to obtain further information, including management recommendations and algorithm-ranked alternatives.

Reports were prepared by laboratory staff. Interactions that were flagged as being of high severity and all interactions that were flagged as having a CYP-related genetic cause were included in the report. Once prepared, these reports were reviewed and authorized by a clinician.

Clinicians reviewed all reports for accuracy and classified the interactions into one of four severity categories (Table 1). These ratings were based on clinical judgment and took into account patient characteristics

Table 2. Demographic and Medication-Use Data on Study Population

Variable	Value
Sex, % (*n* = 22,162)	
Female	57.9
Male	42.1
Race/ethnicity, % (*n* = 15,384)	
Caucasian	68.7
Hispanic	18.0
African-American	11.4
Asian	1.5
Jewish (Ashkenazi)	0.4
Age, yr (*n* = 22,955)	
Range	0.6–108
Mean	60
No. medications per patient[a] (*n* = 20,534)	
Range	1–49
Mean overall	9.1
Mean for patients ≥65 years of age	10.5
Mean for patients ≤64 years of age	7.2

[a]Data are for patients who submitted a medication list. Some medication lists included herbals, nonprescription medications, and vitamins in addition to prescription medications; however, this information was not always available.

provided by the referring provider. "Change" interactions were the most severe and generally included situations wherein drug combinations were contraindicated, duplicate therapy was identified, or literature recommended avoidance (or significant modification) of a particular drug–drug or drug–gene combination (e.g., clopidogrel use by a CYP2C19 poor metabolizer). The remaining interaction severity categories, in order of decreasing severity, were "consider," "monitor," and "no change." The finalized reports were sent to the referring provider as requested via secure Web access, fax, or mail.

Analytic approach. To assess the prevalence of each interaction severity categorization (change, consider, monitor, and no change) within the study population, we examined the interaction types in three ways. First, the distributions of all interaction types (DDI, DGI, and DDGI) were analyzed. Second, the distribution was analyzed with a focus on DDIs alone. Third, the distribution was analyzed with a focus on both DGIs and DDGIs. The subgroup analysis compared data on all patients with data on those 64 years of age or younger and data on those 65 years of age or older.

Results

Referrals came from clinicians in the following medical specialties: family practice (n = 5157, 22.5%), internal medicine (n = 4020, 17.5%), pain (n = 3330, 14.5%), cardiology (n = 2809, 12.2%), and psychiatry (n = 1861, 8.1%). The remaining 25.2% of the referrals (n = 5578) were from other medical specialists, multispecialty practices, and undefined facilities.

Reasons for pharmacogenetic testing referral included

- Long-term current use of other medications (*International Classification of Diseases, Ninth Revision [ICD-9]* code V58.69) (5861 referrals),
- Unspecified adverse effect of drug, medicinal, and biological substances due to correct medicinal substance properly administered (*ICD-9* code 995.2) (2687 referrals),
- Patients with complex medication management needs, including patients with hypertension (*ICD-9* code 401.9) and diabetes (*ICD-9* code 250) (1268 and 908 referrals, respectively),
- Suboptimal treatment benefit,
- Receipt of medications with FDA warnings on DGIs (e.g., clopidogrel), and
- Identification of patient as being at high genetic risk with the YouScript risk assessment tool.

Table 2 describes the demographics of the study population.

Genetic analysis focusing on at least one of the targeted CYP isozymes (CYP2D6, CYP2C19, CYP2C9, CYP3A4, and CYP3A5) was carried out in 22,885 referred patients. Medication histories were available for 20,534 patients in the study population. In the 2,251 cases in which medication histories were not provided, interaction analysis was not carried out, but the genetic data were still included in the phenotype frequency analysis. The majority of interactions involved medications that had already been prescribed, so the reports were usually retrospective in nature. However, in some instances, referring providers requested opinions regarding planned medication prescribing or past treatment failures.

Phenotype frequency. The frequency distribution of the tested phenotypes in the study population is shown in Table 3. For each of the genes of interest, a large fraction of the patients were characterized as having

Table 3. Distribution of Evaluated Cytochrome P-450 (CYP) Metabolic Phenotypes in Study Population

CYP Isozyme and Phenotype	Prevalence (%)
CYP2D6 (n = 22,225)	
Normal metabolizer	52.8
Intermediate metabolizer	37.7
Poor metabolizer	6.8
Ultrarapid metabolizer	2.7
CYP2C9 (n = 22,649)	
Normal metabolizer	67.5
Intermediate metabolizer	29.1
Poor metabolizer	3.4
CYP2C19 (n = 22,725)	
Normal metabolizer	42.1
Ultrarapid metabolizer	29.5
Intermediate metabolizer	25.8
Poor metabolizer	2.6
CYP3A4 (n = 14,615)	
Normal metabolizer	92.4
Intermediate metabolizer	7.6
CYP3A5 (n = 14,596)	
Nonexpresser	72.3
Intermediate expresser	20.5
Expresser	7.2

a "risk phenotype" (i.e., a phenotype associated with interaction risk). The phenotype breakdown, by enzyme, was as follows: 47.1% of evaluated patients were categorized as intermediate, poor, or ultrarapid CYP2D6 metabolizers; 57.9% of evaluated patients were categorized as intermediate, poor, or ultrarapid CYP2C19 metabolizers; 32.5% of evaluated patients were categorized as intermediate or poor CYP2C9 metabolizers; 7.6% of evaluated patients were categorized as intermediate CYP3A4 metabolizers; and 27.7% of evaluated patients were characterized as CYP3A5 intermediate expressers or expressers.

Risk phenotype distribution. With regard to the distribution of risk phenotypes in patients who underwent testing focused on all five CYP isozyme–encoding genes ($n = 14,578$), 7% had no risk phenotypes while 33% had one, 41% had two, 17% had three, and 2% had four risk phenotypes. There were 6 individuals with all five risk phenotypes.

Interaction type prevalence. Of all patients referred for testing, 20,534 had a medication list submitted; the majority of those patients (69.1%) had at least one reported interaction. A total of 33,665 interactions were reported, and 16,924 of those were severe (i.e., rated at a level of "change" or "consider" by study clinicians). Of these severe interactions, 53.0% were DDIs, 24.6% were DGIs, and 22.4% were DDGIs.

Interaction severity analysis. Prevalence data on interaction severity were analyzed for 20,534 patients; 10,727 patients were in the younger group (age of ≤64 years) and 9,807 patients were in the older group. As shown in Table 4, the percentages of patients with at least one "change" interaction were 8.9% for the entire population, 6.7% for the younger group, and 11.4% for the older group. The percentages of patients with at least one "consider" interaction were 36.7% for the entire group, 34.2% for the younger group, and 39.4% for the older group. The percentage change in the frequency of identification of most severe potential interactions between the younger and older groups was 70.1% for "change" interactions and 15.2% for "consider" interactions.

Medication history analysis. While 1,390 unique medications were prescribed for this population of 20,534 patients, a few medications were very commonly prescribed (at a rate of >10%), and some were common interaction offenders. On average, patients in this population were being treated with 9 medications; that figure was higher (10.5) in the older group and lower (7.2) in the younger group (Table 2). Table 5 provides an overview of the medications most

Table 4. Comparative Data on Clinician-Rated Interaction Severity in Study Population, Overall and by Age Group[a]

Severity Category	Frequency of Category Assignment (%)			% Difference (Older vs. Younger Patients)[b]
	All Patients (n = 20,534)	≤64 Years of Age (n = 10,727)	≥65 Years of Age (n = 9,807)	
All interactions (DDIs, DGIs, and DDGIs)[c]				
Change	8.9	6.7	11.4	70.1
Consider	36.7	34.2	39.4	15.2
Monitor	23.5	23.8	23.2	–2.5
No change	30.9	35.3	26.1	–26.1
DDIs only[c]				
Change	5.4	4.5	6.3	40.0
Consider	22.9	19.5	26.6	36.4
Monitor	8.3	6.6	10.1	53.0
No change	63.5	69.4	56.9	–18.0
DGIs and DDGIs only[c]				
Change	3.9	2.5	5.5	120.0
Consider	23.4	22.6	24.2	7.1
Monitor	28.4	27.4	29.5	7.7
No change	44.3	47.5	40.8	–14.1

[a]DDI = drug–drug interaction, DGI = drug–gene interaction, DDGI = drug–drug–gene interaction.
[b]Difference in frequency of category assignment between older and younger age groups.
[c]If a patient had multiple identified interactions, only the interaction with the highest severity rating was considered in the frequency analysis.

commonly flagged as being involved in a DGI or DDGI (or both).

Discussion

We performed an analysis of data on 22,885 patients who were referred for clinical pharmacogenetic and drug interaction management. Our study demonstrated a high prevalence of interaction risk–associated metabolic phenotypes in a mixed-race U.S. population. Among patients who underwent testing focused on all five evaluated CYP isozymes, 93% had two or more risk-associated phenotypes, with high frequencies of intermediate metabolizer status and poor metabolizer status. The high prevalence of risk-associated metabolic phenotypes was found to result in a large proportion of the most severe interactions with a genetic component. In patients with submitted medication lists, 16,924 of the reported interactions reached a severity level of "change" or "consider," and just under half of those (47.0%) had a genetic component. Our findings demonstrated that potentially severe interactions were prevalent in the evaluated population of patients referred for pharmacogenetic testing. For the entire population, the total number of patients with at least one "change" or "consider" interaction due to a DGI or DDGI (n = 5,600) was 27.3%. In addition, the study found that patients who were 65 years of age or older were more likely to benefit from routine CYP isozyme–focused gene testing. In particular, 11.4% of interactions in the older group were "change" interactions, as compared with 6.7% of interactions in the younger group.

The fact that most patients are, apparently, not normal metabolizers is exceedingly important when managing a patient's medications. The wide distribution of CYP isozyme–encoding gene variants suggests that a large number of DGIs and DDGIs will go undetected without genetic testing. Compared with the results of a previous study of CYP genotypes and interaction potential by Verbeurgt et al.,[6] the results of our study indicated a higher proportion of DGIs and DDGIs versus DDIs. Verbeurgt and colleagues reported that 66.1% of the interactions identified in their study were DDIs, 14.7% were DGIs, and 19.2% were DDGIs. When comparing our analysis to that study, a "change" interaction in our study can be considered as equivalent to a "potentially major" interaction in the study of Verbeurgt et al., and a "consider" interaction in our study can be considered as equivalent to a "potentially substantial" interaction by their classification scheme. In our analysis, 24.6% of all "change" and "consider" interactions were DGIs, and 22.4% were DDGIs. The finding of higher rates of "change" and "consider" interactions with a genetic component in our study versus the study of Verbeurgt and colleagues was likely due to a number of factors, including analysis of an increased number of CYPs (unlike the study of Verbeurgt et al., our analysis included *CYP3A4*- and *CYP3A5*-associated interactions); increased awareness of pharmacogenetic-based interactions, leading to more selective patient referral; the availability of more information on pharmacogenetic-based interactions, which resulted in a more robust database; and our study's 18-fold larger population, which may have resulted in data more representative of the general population.

The increased interaction severity among older versus younger patients in our study may have been due to increased drug utilization (patients in the older subgroup were taking an average of 10.5 medications, as compared with an average of 7.2 medications per patient in the younger subgroup) and, consequently, an increased likelihood of more serious potential interactions. However, in the population of patients included in this analysis, the average number of medications

Table 5. Top 10 Medications Involved in Potential Interactions in Study Population[a]

Medication[b]	No. Prescriptions	No. (%) Patients Affected[c]	Primary CYP Metabolic Pathway(s)[13]
Metoprolol	3210	1484 (46)	CYP2D6
Clopidogrel	1906	1415 (74)	CYP2C19
Hydrocodone–acetaminophen	3314	1394 (42)	CYP2D6, CYP3A4[d]
Warfarin	1281	1234 (96)	CYP2C9
Tramadol	1634	743 (45)	CYP2D6
Carvedilol	1363	725 (53)	CYP2D6, CYP2C9[14]
Oxycodone	1425	720 (51)	CYP2D6, CYP3A4
Omeprazole	3031	689 (23)	CYP2C19
Citalopram	1056	606 (57)	CYP2C19[15]
Bupropion	960	531 (55)	CYP2D6[16,e]

[a]CYP = cytochrome P-450.
[b]A medication could be implicated in a potential interaction as either a victim or a perpetrator drug.
[c]Number of patients with at least one detected potential drug–gene or drug–drug–gene interaction (of any severity).
[d]Listed pathways are for hydrocodone only.
[e]The parent form of bupropion is a CYP2B6 substrate, and the metabolite form (hydroxybupropion) is a CYP2D6 substrate. Both the parent form and the metabolite are CYP2D6 inhibitors.

overall was 9.1. The sheer number of patients with risk phenotypes, as well as the prevalence of DGIs and DDGIs identified, suggests that testing may be beneficial in all patients receiving a large number of medications regardless of patient age. The data reported here indicate that patients 65 years and older are at increased risk for harm, which is why specific programs like medication therapy management have been initiated for this age group.

The CYP-pathway characteristics of prescribed medications were important contributors to DGIs and DDGIs in our study. When a medication listed in Table 5 was prescribed, a potential DGI or DDGI was detected a majority of the time. This suggests that the specific metabolism characteristics of medications, especially those listed in Table 5, could be considered as justification for ordering a pharmacogenetic test. Still, it could be argued that routine testing to determine a patient's baseline CYP phenotype status is ideal due to the high prevalence of phenotype variation and the fact that so many medications are metabolized by CYP pathways.

There were limitations to this study. It was a descriptive, hypothesis-generating retrospective analysis. Also, while the analysis focused on a large mixed-race U.S. population, the reported phenotype frequencies and distributions are for patients who were on multiple medications and were referred for testing. Therefore, the analysis may have yielded higher estimates of risk phenotype frequency and distribution than would have resulted from a randomized investigation.

Conclusion

In a mixed-race population of over 20,000 U.S. patients, CYP gene polymorphisms associated with DDIs and other interaction threats were prevalent, and most individuals were not categorized as normal metabolizers of all five CYP isozymes of interest.

Disclosures

Dr. Hocum, Dr. Heck, Dr. Thirumaran, Mr. Moyer, Mr. Newman, and Ms. Ashcraft are employed by Genelex Corporation. The other author has declared no potential conflicts of interest.

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