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Concordance Between Commercial Pharmacogenetic Test Recommendations and CPIC Guidelines for Antidepressant Therapy

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ABSTRACT

Pharmacogenetic testing is increasingly used to guide clinicians in selecting medications tailored to a patient's genetic profile. Although various government-supported organizations aim to establish standardized guidelines for testing and interpretation, adherence to these best practices is often inconsistent. Many pharmacogenetic testing companies rely on proprietary methods for analyzing and reporting results, which can result in inconsistencies across companies and potential differences in how results are interpreted. This study aimed to assess how commercial pharmacogenetic testing vendors differ in translating genotypes to phenotypes and in generating medication recommendations compared with Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines. We performed a retrospective chart review in a large rural healthcare system that utilizes two approved pharmacogenetic testing companies. A total of 100 patients were included, evenly split between the two vendors. Analysis focused on CYP2B6, CYP2C19, and CYP2D6 genes. Medication recommendations for key drug-gene pairs—sertraline (CYP2B6/CYP2C19), escitalopram (CYP2C19), and paroxetine (CYP2D6)—were compared to CPIC guidance, incorporating updates from the 2023 SSRI guideline. To standardize comparison, we developed a three-tier binning system reflecting CPIC-based actions: green for no changes needed, yellow for monitoring suggested, and red for interventions or alternative therapy recommended. This approach allowed systematic evaluation of concordance between commercial reports and guideline-based recommendations. Among the 250 genotype-to-phenotype translations analyzed, 32 (12.8%) differed from CPIC guideline interpretations, all originating from Company A. When examining 266 binned medication recommendations, 114 (42.9%) showed discrepancies between the commercial reports and CPIC guidelines. Breaking this down by vendor, Company A accounted for 93 of the discrepancies, while Company B accounted for 21, as determined using the novel binning system. Notable differences were identified between the interpretations and recommendations of the two pharmacogenetic testing companies, raising concern that such discrepancies could prompt providers to make medication decisions that deviate from CPIC clinical practice guidelines. This misalignment may contribute to suboptimal patient outcomes, decreased satisfaction for both patients and providers, and diminished trust in pharmacogenetic testing. To address these inconsistencies, greater adherence to CPIC guidelines and increased transparency in interpretation methods are recommended.

Keywords: Pharmacogenomics, Pharmacogenetic testing results, Pharmacogenetic testing company, Binning, pharmacogenetics, Pharmacogenetic testing

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Introduction

In recent years, clinicians have increasingly relied on pharmacogenetic testing to optimize medication therapy, particularly for drug-gene pairs—combinations of specific drugs and genes that may influence the pharmacokinetics or pharmacodynamics of a medication. Pharmacogenetic testing identifies genetic variants, and when a drug-gene interaction (DGI) is detected, it suggests that a patient's genetic profile could alter the drug's therapeutic effect. With many commercial vendors offering pharmacogenetic testing, assessing differences in how

companies interpret drug-gene pairs and DGIs can be challenging. While regulations exist for laboratory-developed tests (LDTs), which are commonly used in pharmacogenetic testing, enforcement and standardization have historically been limited [1]. The FDA is currently revising its "enforcement discretion" approach for LDTs, though proposed changes and implications remain under discussion [2].

Efforts to standardize pharmacogenetic testing and guide clinical use have been led by NIH-supported organizations such as the Clinical Pharmacogenetic Implementation Consortium (CPIC), PharmGKB, the Pharmacogene Variation (PharmVar) Consortium, and professional groups like the Association for Molecular Pathology (AMP). The FDA also contributes resources supporting drug-gene pairs, including the table of Pharmacogenetic Associations. CPIC, an international consortium adhering to Institute of Medicine standards for guideline development, provides evidence-based recommendations for healthcare professionals on pharmacogenetic testing, with rigorous conflict-of-interest management [3-5]. PharmGKB curates drug-gene pairs and genotype-to-phenotype relationships, hosting CPIC and other professional guidelines, while PharmVar maintains consensus allele definitions for pharmacogenes. AMP has developed standards specifying the minimum variants to include in pharmacogenetic panels. All NIH-supported organizations grade and rate evidence for their recommendations using transparent criteria. CPIC links genotype-to-phenotype data with levels of evidence (high, moderate, weak) and provides therapeutic recommendations ranked by strength (strong, moderate, optional). PharmGKB employs an annotation scoring system for clinical and variant annotations (Levels 1A–4), and PharmVar provides evidence levels for allele-haplotype definitions, reflecting the quantity and nature of data supporting each definition rather than the data quality itself [6, 7]. The FDA provides multiple pharmacogenetic resources, including the table of Pharmacogenomic Biomarkers in Drug Labeling and relevant prescribing information, though the sources of this information are sometimes unclear, as they are often submitted by drug manufacturers rather than derived directly from primary literature [8].

These resources are essential for standardizing pharmacogenetic testing, ensuring results can inform evidence-based clinical decisions while minimizing commercial bias. In support of this goal, the AMP Pharmacogenetic Working Group has issued consensus recommendations identifying which alleles all pharmacogenetic laboratories should test. Tier 1 alleles represent the core set that should be included on all platforms, while Tier 2 alleles are recommended supplements [9]. Although AMP's tiers do not carry formal evidence levels, they provide clear criteria for classification, drawing heavily on guidance from NIH-supported organizations [10]. Currently, AMP guidelines cover seven genes, with additional genes expected in the future. Around the same period, several studies reported substantial variability in gene and allele evaluation across commercial laboratories [1, 11], likely reflecting the use of proprietary algorithms and interpretation methods. Notably, no regulatory body mandates adherence to these standards, leaving discrepancies unresolved despite available guidance. While such variability may appear minor, it can have significant therapeutic implications: medication recommendations may be influenced more by a company's proprietary algorithm than by a patient's actual genetic profile. No multi-gene proprietary algorithm has been validated or endorsed by the FDA or CPIC. Discrepancies between commercial testing companies and CPIC for genotype-to-phenotype translation have been documented [12], as has variability in medication recommendations based on genotype across companies [11]. Many laboratories continue to rely on proprietary methods for reporting results and formulating recommendations [1, 11, 13]. In response, the FDA issued warnings to patients and providers in 2018 and subsequently to testing companies in 2019, noting the lack of credible data supporting these medication recommendations [14, 15]. Pharmacogenetic companies rarely publish data demonstrating the clinical validity or utility of their algorithms, and when they do, methodological limitations, absence of durable clinical outcomes, or weak evidence reduce confidence in their conclusions [11, 16-18]. Interpretation through proprietary "combinatorial" algorithms may lead clinicians to deviate from evidence-based guidelines [19]. The lack of transparency in these algorithms has been described as a "black box" in pharmacogenetic clinical decision support, posing potential risks to users regarding the clinical validity of recommendations [20]. Although the implications of genotype-to-phenotype and medication recommendation discrepancies may not be immediately apparent, divergence from trusted, evidence-based guidance carries real risks. At best, proprietary recommendations may misrepresent drug-gene interactions and erode clinician trust and satisfaction with pharmacogenetics; at worst, they may jeopardize patient safety by basing therapeutic decisions on lower-quality data.

This study seeks to build on prior work by evaluating medication recommendation discrepancies relative to CPIC guidelines using a novel binning system. The system categorizes drug-gene interactions into three levels, allowing comparison of commercial proprietary algorithm outputs with evidence-based recommendations.

Materials and Methods

Study design and participants

A retrospective chart review was conducted on a random sample of patients who underwent pharmacogenetic testing between July 1, 2018, and December 31, 2023, as part of a pharmacy postgraduate year-1 residency project. The analysis focused on patients tested by one of two institution-approved pharmacogenetic vendors: GeneSight™ (Company A) and OneOme™ (Company B), both of which employ deletion/duplication detection alongside targeted variant analysis. Inclusion required only completion of pharmacogenetic testing, encompassing test ordering, specimen collection, analysis, and report availability in the electronic medical record within the study period. Patient age was not considered an exclusion factor, as genetic variants remain constant across age groups, and resulting medication recommendations are generally applicable to pediatric populations [21]. Eligible patients were identified in sequential blocks by a data analyst or pharmacist until 50 patients per vendor were included. Each vendor group included 25 patients tested before and 25 after the 2023 CPIC Serotonin Reuptake Inhibitor (SSRI) guideline update to ensure temporal representation. All pharmacogenetic results were reviewed by a pharmacist with specialized expertise in pharmacogenetics. Actionable alleles, genotypes, and phenotypes for CYP2B6, CYP2C19, and CYP2D6 were determined according to CPIC guidelines. To compare medication recommendations between vendors and CPIC, a three-tier internal binning system based on the CPIC SSRI guideline was implemented **(Tables 1 and 2)**. The study protocol was reviewed and classified as exempt from full IRB review under quality improvement criteria by the Marshfield Clinic Institutional Review Board.

Table 1. Definitions and general recommendations for binning system categories.

Bin	Level of Drug-Gene Interaction (DGI)	Description	Recommended Action	Illustrative CPIC Guidance
Bin 1 (Green)	Minimal / Unknown	Interaction is absent, negligible, or lacks sufficient evidence to suggest altered metabolism, adverse effects, or reduced efficacy.	Follow standard FDA dosing; no special intervention needed.	"Begin therapy at the recommended starting dose." "No recommendation provided due to limited evidence."
Bin 2 (Yellow)	Moderate	Interaction has a modest impact on drug metabolism or indicates a slight increased risk of adverse effects or reduced therapeutic effect.	Initiate at usual dose and monitor; adjust dosing if clinically indicated.	"Start at the recommended dose. Consider slower titration and a lower maintenance dose compared to normal metabolizers."
Bin 3 (Red)	Significant / Major	Interaction meaningfully alters drug metabolism or carries a high risk of adverse reactions or treatment failure.	Either select an alternative drug or modify the dose carefully.	"If using citalopram or escitalopram, start at a reduced dose, titrate slowly, and reduce maintenance dose by 50% relative to normal metabolizers." "Choose an alternative medication not primarily metabolized by CYP2D6."

This binning system classifies SSRI drug-gene-phenotype interactions into three color-coded categories based on CPIC SSRI guideline recommendations, including the 2023 update. Bin 1 (green) indicates no clinically significant interaction and requires no action. Bin 2 (yellow) represents a moderate interaction, warranting monitoring and possible dose adjustment. Bin 3 (red) reflects a major interaction, suggesting an alternative therapy or significant dose modification.

Table 2. Novel Binning System for SSRI Drug-Gene Pairs

	UM	RM	NM	IM	PM
CPIC guidelines before 4/10/2023					
Sertraline and *CYP2C19*	Bin 2	Bin 2	Bin 1	Bin 1	Bin 3

Escitalopram and *CYP2C19*	Bin 3	Bin 3	Bin 1	Bin 1	Bin 3
Paroxetine and *CYP2D6*	Bin 3	NA	Bin 1	Bin 1	Bin 3
CPIC guidelines on or after 4/10/23					
Sertraline and *CYP2B6*	Bin 1	Bin 1	Bin 1	Bin 2	Bin 2
Escitalopram and *CYP2C19*	Bin 3	Bin 2	Bin 1	Bin 2	Bin 3
Paroxetine and *CYP2D6*	Bin 3	NA	Bin 1	Bin 2	Bin 3

Abbreviations: UM, ultrarapid metabolizer; RM, rapid metabolizer; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; NA, not applicable.

Objectives

This quality improvement project aimed to examine two key areas: first, how commercial pharmacogenetic testing companies translate genotypes into phenotypes, and second, how their behavioral health medication recommendations align—or differ—from CPIC guideline guidance.

Novel binning process

Commercial pharmacogenetic testing companies often use their own criteria to categorize the clinical impact of drug-gene interactions (DGIs) in patient reports. These categorizations are frequently presented using a three-tier, traffic light system: green for minimal or no interaction, yellow for moderate interaction, and red for major interaction. To facilitate direct comparison between commercial reports and CPIC guidelines, our institution developed a novel binning system that also follows the traffic light convention. This system aligns with CPIC recommendations, classifying each medication recommendation according to the clinical significance of the DGI, enabling standardized comparison to vendor-provided bins **(Tables 1 and 2)**. In this framework, Bin 1 (green) corresponds to recommendations that follow standard dosing, Bin 2 (yellow) reflects situations where the standard starting dose applies but monitoring or dose adjustment may be needed, and Bin 3 (red) indicates either avoidance of the drug or initiation with adjusted dosing and additional monitoring.

For this study, behavioral health medications included in both CPIC guidelines and commercial reports were selected for analysis: escitalopram, paroxetine, and sertraline. Bin assignments were based on relevant CPIC SSRI guideline recommendations for the corresponding drug-gene pairs: sertraline with CYP2C19 (pre-guideline update) or CYP2B6 (post-update), escitalopram with CYP2C19, and paroxetine with CYP2D6 [21, 22]. Notably, post-update sertraline recommendations considered both CYP2B6 and CYP2C19; only patients with CYP2C19 wild-type status were included to isolate the CYP2B6 effect. Commercially reported bin assignments for these drug-gene pairs were then compared to the novel binning system to identify any discrepancies between vendor reports and CPIC-based recommendations.

Timeline of CPIC's serotonin reuptake inhibitor antidepressants guideline

The CPIC SSRI guideline was originally published in 2015 [22] and subsequently updated in April 2023 [21], which was taken into account during data collection and analysis **(Figure 1)**. To accommodate the update, patients with pharmacogenetic report dates on or before April 9, 2023, were analyzed separately from those with report dates on or after April 10, 2023. The 2015 guideline identified only CYP2C19 as influencing sertraline metabolism, whereas the 2023 update recognized both CYP2C19 and CYP2B6 as relevant [21]. April 10 was selected as the cutoff because PharmGKB implemented the guideline update on that date, as documented in their history records. While pharmacogenetic testing companies may not update their reports immediately following guideline changes, there is currently no standardized timeframe for updating medication recommendation algorithms. For consistency and simplicity, the PharmGKB release date was used as the reference point for this analysis.

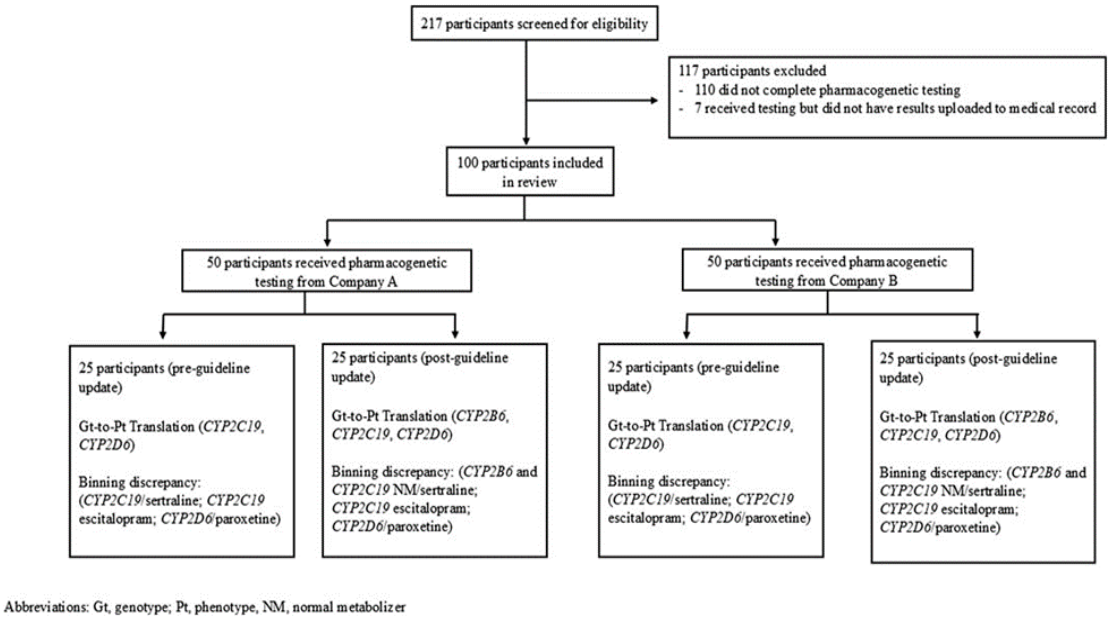

Figure 1. Enrollment.

For the evaluation of genotype-to-phenotype translations, the genes CYP2B6, CYP2C19, and CYP2D6 were selected, as both Company A and Company B report on these and CPIC provides corresponding translation tables. For patients with pharmacogenetic reports dated on or before April 9, 2023, analyses followed the 2015 CPIC guidelines, focusing on CYP2C19 and CYP2D6. Medication recommendations were assessed for CYP2D6 with paroxetine and CYP2C19 with escitalopram and sertraline **(Figure 1)**. For reports issued after the guideline update, the assessment included all three genes—CYP2B6, CYP2C19, and CYP2D6—and evaluated drug-gene pairs consisting of CYP2B6 with sertraline, CYP2C19 with escitalopram, and CYP2D6 with paroxetine **(Figure 1)**. Although CYP2D6 also affects fluvoxamine according to the 2015 CPIC guidelines, paroxetine was chosen due to its greater prescription prevalence at our institution.

Statistical analysis

Patient data were extracted using SAS and analyzed qualitatively. No statistical testing was performed, as the study aimed solely to evaluate each pharmacogenetic testing company individually and report descriptive findings.

Results and Discussion

Evaluated population

Although patient ancestry or ethnic background was not recorded, the healthcare system primarily serves individuals of Western European descent. A total of 217 patients were initially screened to achieve the target sample size, with 117 excluded due to incomplete pharmacogenetic testing (e.g., tests ordered but not completed) or unavailable results in the medical record **(Figure 1)**. The final analysis included 100 patients, evenly divided between the two testing companies. Within each company, 25 patients had testing completed before the updated CPIC guidelines, and 25 patients had testing completed after the guideline update.

Genotype-to-phenotype translation

Among the 50 patients tested prior to the updated CPIC guidelines, two genes (CYP2C19 and CYP2D6) were evaluated, resulting in 100 genotype-to-phenotype translations. For the 50 patients tested after the guideline update, three genes (CYP2B6, CYP2C19, and CYP2D6) were analyzed, yielding 150 translations. Across both companies, a total of 250 genotype-to-phenotype translations were reviewed, of which 32 (12.8%) were discordant with CPIC recommendations, all originating from Company A. The majority of discrepancies involved CYP2C19 (17 cases, 53.1%), followed by CYP2D6 (13 cases, 40.6%) and CYP2B6 (2 cases, 6.3%) **(Table 3)**. The most frequently discrepant genotypes were CYP2C19 *1/*17 (seven instances pre- and seven post-guideline update) and CYP2D6 *2A/*4 (five pre- and three post-guideline update) for Company A. No genotype-to-phenotype discrepancies were observed for Company B.

Table 3. Company genotype-to-phenotype translation comparison discrepancies.

Gene	Genotype	Percentage % (n)	Company phenotype	CPIC phenotype
Company A – 32 discrepancies				
CYP2B6	2 discrepancies (6.3%)			
	*1/*4	100 (2)	UM	RM
CYP2C19	17 discrepancies (53.1%)			
	*1/*17	82.4 (14)	NM	RM
	*2/*17	17.6 (3)	NM	IM
CYP2D6	13 discrepancies (40.6%)			
	*2A/*2A	23.1 (3)	UM	NM
	*2A/*4	61.5 (8)	NM	IM
	*2A/*5	7.7 (1)	NM	IM
	*4/*41	7.7 (1)	PM	IM
Company B – 0 discrepancies				

Abbreviations: UM, ultrarapid metabolizer; RM, rapid metabolizer; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

Drug-gene pairs evaluation

Overall evaluation

In total, 266 drug-gene pairs were assessed across the 100 patients in this study. Of these, 152 pairs (57.1%) were consistent with CPIC SSRI guideline recommendations, while 114 pairs (42.9%) showed discrepancies **(Figure 2).** For the 50 patients tested before the guideline update (25 per company), three drug-gene pairs per patient were reviewed, resulting in 75 pairs. After the guideline update, sertraline recommendations were analyzed only for patients who were CYP2C19 normal metabolizers to isolate the effect of CYP2B6, yielding 24 pairs (eight patients per company, three pairs each: CYP2B6/sertraline, CYP2C19/escitalopram, CYP2D6/paroxetine). For the remaining 34 patients who were CYP2C19 non-normal metabolizers, only CYP2C19/escitalopram and CYP2D6/paroxetine were assessed, adding 34 pairs. Overall, this produced 133 medication recommendations per company. Company A had 93/133 (70%) recommendations that diverged from CPIC, whereas Company B had 21/133 (15.8%) discrepancies **(Table 4 and Figure 2)**.

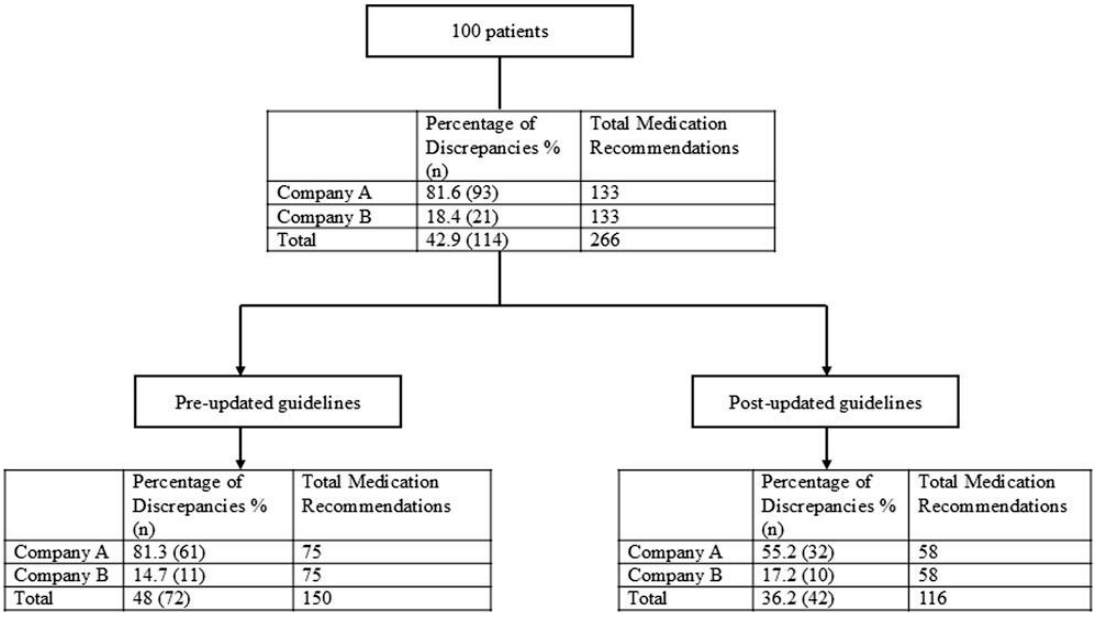

Figure 2. Overall medication recommendation evaluation and results.

Table 4. Overall medication recommendation concordance comparison.

	Percentage of congruencies % (n)	Percentage of discrepancies % (n)	Total
Company A	30 (40)	70 (93)	100 (133)
Company B	84.2 (112)	15.8 (21)	100 (133)

Prior to CPIC SSRI guideline update

Among the 50 patients tested before the updated CPIC guidelines (25 per company), three drug-gene pairs—escitalopram/CYP2C19, sertraline/CYP2C19, and paroxetine/CYP2D6—were analyzed, representing 150 drug-gene pairs in total (75 per company). In Company A, 61 of 75 medication recommendations (81.3%) diverged from the novel binning system **(Table 5 and Figure 2)**. These discrepancies were distributed as follows: 22 (36.1%) for escitalopram/CYP2C19, 22 (36.1%) for paroxetine/CYP2D6, and 17 (27.8%) for sertraline/CYP2C19 **(Table 6)**. The genotypes most frequently involved were CYP2C19 *1/*1 and *1/*17 for escitalopram, CYP2D6 *1/*4 and *2A/*4 for paroxetine, and CYP2C19 *1/*1 for sertraline. For Company B, 11 of 75 recommendations (14.7%) were inconsistent with the novel binning system, primarily affecting paroxetine and sertraline. Only one discrepancy was noted for escitalopram (CYP2C19 *1/*17). Paroxetine/CYP2D6 had five discordant recommendations—two each for *1/*4+*68 and *2A/*4+*68, and one for *3/*9—while sertraline/CYP2C19 discrepancies involved genotypes *1/*1 and *1/*2 **(Table 6).**

Table 5. Medication recommendation comparison for patients receiving testing prior to updated CPIC guideline.

	Percentage of congruencies % (n)	Percentage of discrepancies % (n)	Total
Company A	18.7 (14)	81.3 (61)	100 (75)
Company B	85.3 (64)	14.7 (11)	100 (75)

Table 6. Frequency of genotypes with discrepant medication recommendations for patients receiving testing prior to updated CPIC guidelines.

Drug-gene pair	Genotype	Percentage % (n)
Company A – 61 discrepancies		
Escitalopram and *CYP2C19*	22 discrepancies	
	*1/*1	45.5 (10)
	*1/*17	31.8 (7)
	*1/*2	13.6 (3)
	*2/*17	9.1 (2)
Paroxetine and *CYP2D6*	22 discrepancies	
	*1/*1	9.1 (2)
	*1/*2A	13.7 (3)
	*1/*3	9.1 (2)
	*1/*4	18.2 (4)
	*1/*41	4.5 (1)
	*1/*5	4.5 (1)
	*2A/*2A	9.1 (2)
	*2A/*4	18.2 (4)
	*2A/*41	4.5 (1)
	*2A/*9	9.1 (2)
Sertraline and *CYP2C19*	17 discrepancies	
	*1/*1	58.9 (10)
	*1/*17	5.9 (1)

	*1/*2	17.6 (3)
	*17/*17	5.9 (1)
	*2/*17	11.7 (2)
Company B – 11 discrepancies		
Escitalopram and *CYP2C19*	1 discrepancy	
	*1/*17	100 (1)
Paroxetine and *CYP2D6*	5 discrepancies	
	*1/*4+*68	40 (2)
	*2A/*4+*68	40 (2)
	*3/*9	20 (1)
Sertraline and *CYP2C19*	5 discrepancies	
	*1/*1	40 (2)
	*1/*2	60 (3)

Following the CPIC SSRI guideline update

Among the 50 patients tested after the updated CPIC guidelines were posted on PharmGKB, 16 patients (eight per company) were CYP2C19 normal metabolizers. For these patients, three drug-gene pairs—sertraline/CYP2B6, escitalopram/CYP2C19, and paroxetine/CYP2D6—were assessed, yielding 48 drug-gene pairs in total. The remaining 34 patients (17 per company) were CYP2C19 non-normal metabolizers, and two drug-gene pairs—escitalopram/CYP2C19 and paroxetine/CYP2D6—were evaluated, totaling 68 pairs. In sum, 116 medication recommendations (58 per company) were analyzed for patients with post-guideline test reports. Company A had 32 of 58 recommendations (55.2%) that were discordant with the binning system, primarily affecting CYP2C19/escitalopram (15/32, 46.9%) and CYP2D6/paroxetine (14/32, 43.8%) **(Table 8)**. Discrepancies for escitalopram/CYP2C19 most often involved genotypes *1/*1 and *1/*2, while paroxetine/CYP2D6 discrepancies were frequently *1/*2A and *2A/*4. Company B had 10 of 58 recommendations (17.2%) that were discordant, with 8/10 (80%) for escitalopram/CYP2C19 and 2/10 (20%) for sertraline/CYP2B6. The genotypes involved in these discrepancies were *1/*17 and *1/*2 for escitalopram/CYP2C19 and *1/*6 for sertraline/CYP2B6 **(Table 8 and Figure 2)**.

Table 7. Medication recommendation comparison for patients receiving testing after updated CPIC guidelines.

	Percentage of congruencies % (n)	**Percentage of discrepancies % (n)**	**Total**
Company A	44.8 (26)	55.2 (32)	100 (58)
Company B	82.8 (48)	17.2 (10)	100 (58)

Table 8. Frequency of genotypes with discrepant medication recommendations for patients receiving testing after up

Drug-gene pair	**Genotype**	**Percentage % (n)**
Company A – 32 discrepancies		
Escitalopram and *CYP2C19*	15 discrepancies	
	*1/*1	53.3 (8)
	*1/*17	13.3 (2)
	*1/*2	26.7 (4)
	*17/*17	6.7 (1)
Paroxetine and *CYP2D6*	14 discrepancies	
	*1/*2A	21.5 (3)

	*1/*4	7.1 (1)
	*1/*41	14.4 (2)
	*2/*2A	7.1 (1)
	*2A/*10	7.1 (1)
	*2A/*2A	7.1 (1)
	*2A/*4	21.5 (3)
	*2A/*5	7.1 (1)
	*4/*41	7.1 (1)
Sertraline and *CYP2B6*	3 discrepancies	
	*1/*1	66.7 (2)
	*1/*4	33.3 (1)
Company B – 10 discrepancies		
Escitalopram and *CYP2C19*	8 discrepancies	
	*1/*17	50 (4)
	*1/*2	50 (4)
Paroxetine and *CYP2D6*	0 discrepancies	
Sertraline and *CYP2B6*	2 discrepancies	
	*1/*6	100 (2)

Variable binning for the same genotype and drug-gene pair

There were 18 instances in which the same genotype for a given drug-gene pair was assigned different medication recommendations across patients. Seventeen of these occurred with Company A and only one with Company B. For Company A, variability was observed in both CYP2C19 and CYP2D6. Specifically, CYP2C19 *1/*17 for escitalopram was categorized as "minimal/limited" in three cases but "moderate" in the remaining ones. Escitalopram/CYP2C19 *1/*2 showed a split between "moderate" (three cases) and "major" for the rest. Paroxetine/CYP2D6 demonstrated inconsistent classifications across genotypes *1/*2A, *1/*3, *1/*4, and *1/*41, roughly half assigned "moderate" and half "major." CYP2D6 *2A/*4 exhibited three different bins: "minimal/limited," "moderate," and "major." Company B had only one variable case: CYP2C19 *1/*17 with escitalopram was binned "moderate" once, otherwise consistently "major."

Trends in "level of impact" of binning

Of the 114 identified discrepancies in medication recommendations, 95 cases (83.3%) were assigned by the companies to a higher-impact bin than indicated by the CPIC-based novel system (Company A = 81, Company B = 14). The remaining 19 discrepancies (16.7%) were rated at a lower level of impact than the CPIC reference (Company A = 12, Company B = 7). In other words, in most cases the companies' reports suggested a stronger drug-gene interaction than CPIC guidance, whereas in a smaller subset the CPIC-aligned bin indicated a more clinically significant interaction than the company-assigned bin.

Our findings corroborate previous reports of discrepancies in how pharmacogenetic testing companies translate genotypes into phenotypes, particularly for CYP2C19 and CYP2D6 [12]. As expected, these differences in genotype-to-phenotype interpretation lead to corresponding divergences in medication recommendations when compared with CPIC guidelines. These discrepancies were evaluated using a novel binning system designed to reflect CPIC's recommendations, maintaining consistency with CPIC's language and action-oriented guidance. Even with this standardized framework, substantial differences between company interpretations and CPIC recommendations were observed.

The use of proprietary algorithms contributes not only to inconsistencies between testing companies and professional standards like CPIC, but also to variability across companies themselves. For instance, a comparison of four commercial pharmacogenetic testing companies found that only CYP2C9 achieved complete congruency in genotype-to-phenotype translation. Other genes, such as CYP2C19, CYP3A4, and UGT2B15, showed perfect

genotype agreement but divergent phenotype assignments, with congruency ranging from 33% to 89% [11]. Overall, only 58% of medication recommendations were concordant among the companies, while 71% of genotypes aligned.

Similarly, Blazy *et al*. reported discrepancies of 28.8% for CYP2D6 and 32.2% for CYP2C19 when comparing one company's genotype-to-phenotype translations to CPIC standards [12]. Specific genotypes associated with these inconsistencies, including CYP2D6 *2A/*2A, *2A/*4, *4/*41 and CYP2C19 *1/*17, were consistent with the patterns observed in our study. Given these ongoing incongruencies, transparency in how laboratories convert genotypes to phenotypes and subsequently generate medication recommendations is essential. Clear reporting practices allow clinicians and implementers of pharmacogenetics to understand the basis of recommendations and apply them safely in clinical care [23].

To our knowledge, this study is the first to document instances in which different pharmacogenetic testing companies provided conflicting medication recommendations for the same genotype within the same drug-gene pair. These inconsistencies were observed most frequently for escitalopram and paroxetine, with most discrepancies classified in the moderate (yellow) or major (red) bins. Proprietary algorithms may contribute to this variability by incorporating additional genes into the assessment of medication response; however, these approaches are not aligned with CPIC guidelines. Such discrepancies could lead providers to unnecessarily exclude a potentially beneficial therapy. In mental health care, inappropriate exclusion of familiar and generally well-tolerated medications like paroxetine or escitalopram may prompt escalation to alternative treatments, potentially increasing costs, adverse effects, and monitoring burden. These findings underscore the importance of standardizing pharmacogenetic interpretation to maintain provider confidence and ensure appropriate clinical use of test results.

Medication recommendation discrepancies are not exclusive to company versus guideline comparisons; differences have also been reported among government and professional guidelines [8, 24, 25]. Professional guidelines generally benefit from transparent development processes [3], access to comprehensive data, and safeguards against conflicts of interest. Discrepancies between guidelines are often attributable to differences in scope, methodology, or the timing of recommendations [8].

Binning of drug-gene interactions is widely used in clinical pharmacotherapy to facilitate interpretation. In this study, a novel color-coded binning system was developed to allow comparison of commercial testing company recommendations with CPIC guidance. While intuitive and user-friendly, binning has limitations: it may oversimplify recommendations, potentially discouraging use of appropriate medications that could be safely managed with dose adjustments or monitoring. Color-coded bins may also be inaccessible to colorblind users. Additionally, some commercial panels include genes without CPIC guidelines, potentially reflecting commercial rather than clinical priorities. Standardization of binning practices within the pharmacogenetic community could enhance clarity, improve guideline adherence, and support broader adoption of pharmacogenetic testing in clinical care.

This real-world evaluation has several limitations. The sample size was modest and drawn from a single rural health system, which has unique features in its integration of pharmacogenetic testing into the electronic medical record, including clinical decision support for Company B. The study spanned a five-year period during which technology and testing practices evolved; as a result, changes in company platforms, such as methodology or variant coverage, may not have been fully captured. Additionally, transitions in the health system's electronic medical record and ordering workflows between 2021 and 2023 may have affected patient identification.

The exact sources that Company A and Company B rely upon for generating medication recommendations are not publicly disclosed. Therefore, assumptions regarding the timing of the CPIC SSRI guideline update and its influence on company recommendations may not fully reflect actual practices. If the guideline update did influence recommendations, it is important to recognize that companies may require time to incorporate changes into their algorithms. Conversely, some pharmacogenetic testing company staff may anticipate guideline updates, particularly if they are CPIC members, potentially allowing earlier integration. While other reputable resources exist for pharmacogenetic interpretation, this study focused solely on CPIC to streamline comparisons using the novel binning system.

Conclusion

In conclusion, discrepancies between commercial pharmacogenetic testing companies and CPIC guidelines were identified for both genotype-to-phenotype translations and medication recommendations, including variable recommendations for the same genotype and drug-gene pair within the same company. These findings are concerning, as proprietary practices could lead providers to make medication decisions that diverge from evidence-based guidelines, potentially resulting in suboptimal patient outcomes and dissatisfaction among both patients and providers. Adherence to CPIC guidelines represents a potential path toward harmonizing interpretations. Future work may benefit from comparative analyses of commercial testing recommendations against FDA resources, such as the Table of Pharmacogenetic Associations, to further evaluate consistency and clinical reliability.

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