

Combinatorial Pharmacogenomic Algorithm is Predictive of Sertraline Metabolism in Patients with Major Depressive Disorder

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INTRODUCTION

- Pharmacogenomic testing can aid in treatment selection for patients with Major Depressive Disorder (MDD) by identifying gene-drug interactions that may impact medication metabolism.
- The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides recommendations for sertraline dosing based on genetic phenotypes for *CYP2C19*; however, other groups suggest that additional enzymes may be important for sertraline metabolism.¹
- Although there have been rapid advancements in this field, there is not a consensus about the approach to pharmacogenomic (PGx) testing or even which genes are relevant for many antidepressants.
- Here, we assessed the ability of pharmacokinetic (PK) genes in a combinatorial PGx test (weighted assessment of multiple genes) to predict meaningful variations in sertraline blood levels.

METHODS

COHORT

- All patients were enrolled in the **Genomics Used to Improve DEpression Decisions (GUIDED)** trial – a large, patient- and rater-blinded, randomized, controlled trial that included patients diagnosed with MDD who had an inadequate response to ≥1 psychotropic medication (N=1,167).²
- All patients received combinatorial pharmacogenomic testing as part of the trial.
- A subset of 124 patients reported taking sertraline within 2 weeks of the screening blood draw and had sertraline blood concentrations quantified using LC-MS/MS.

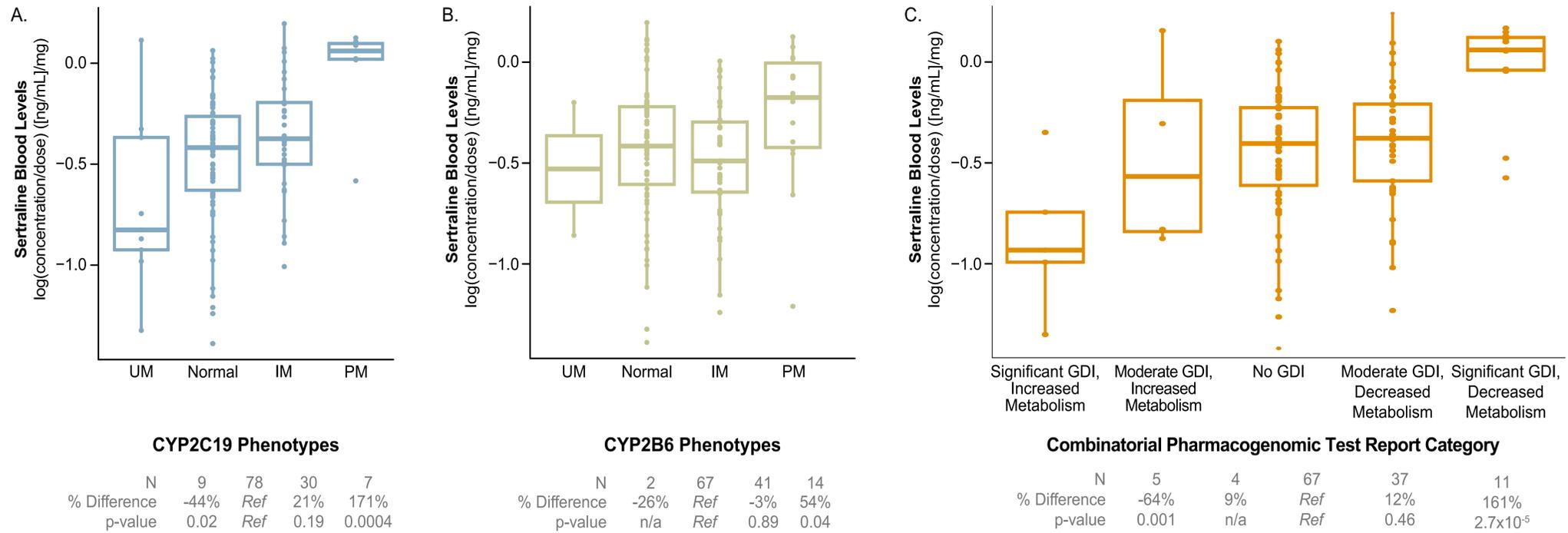
STATISTICAL ANALYSIS

- A combined phenotype for sertraline pharmacokinetics was generated from a weighted, combinatorial algorithm that included *CYP2C19*, *CYP2B6*, and *CYP3A4* to predict the level of gene-drug interactions (GDI) and change in metabolism (increase or decrease).
- The ability to predict variation in sertraline blood levels (log-transformed concentration/dose ratios) was evaluated for:
 - Individual gene phenotypes as defined by the combinatorial PGx test (*CYP2C19*, *CYP2B6*, and *CYP3A4*)
 - Combinatorial PGx** combined phenotype
- All data were analyzed using ANCOVA tests with log-transformed lean body weight as a covariate.

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Figure 1. Sertraline blood levels across phenotypes for individual genes and the combinatorial PGx test.

Boxplots of the log-transformed concentration/dose ratios according to (A) individual *CYP2C19* phenotypes, (B) individual *CYP2B6* phenotypes, or (C) **combinatorial PGx** test phenotypes. The median (thick horizontal line) interquartile range (box) with plus/minus 1.5x interquartile range (vertical lines) are shown.



Abbreviations: PGx, pharmacogenomic; UM, ultrarapid metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; GDI, gene-drug interactions; n/a, not applicable because there were fewer than 5 observations

- Individually, *CYP2C19* and *CYP2B6* predicted blood levels with clinically meaningful differences for poor metabolizers.
- There were no differences observed in metabolizer status for *CYP3A4*.
- Individually, the **combinatorial PGx** test also predicted blood levels.
- Compared to no GDI, clinically meaningful differences (>50%) in blood levels were observed when the **combinatorial PGx** test predicted a significant GDI with both increased metabolism, and decreased metabolism.

Table 1. A multivariate analysis evaluating the ability of individual genes and the combinatorial PGx test to predict variation in sertraline blood levels.

Variables included in Model	Individual Gene		Combinatorial PGx Test	
	F Statistic	p-value	F Statistic	p-value
CYP2C19 and Combinatorial PGx	0.06	0.80	12.3	0.0007
CYP2B6 and Combinatorial PGx	0.23	0.63	27.2	7.9x10 ⁻⁷

The trends in Figure 1 are reflected in this multivariate analysis. After adjusting for all variables in the model, only the **combinatorial PGx** test remained a significant predictor of sertraline blood levels.

DISCUSSION

- Clinically meaningful differences in sertraline blood levels were observed between phenotypes for both *CYP2C19* and *CYP2B6*, suggesting that both enzymes are important for sertraline metabolism.
- Multivariate analyses revealed that the **combinatorial PGx** test accounted for more variance than individual genes alone, and thus was a superior predictor of medication blood levels. This aligns with previous findings across other psychiatric medications.
- Collectively, our findings suggest that the combinatorial PGx test may provide more clinically relevant information to inform decisions regarding sertraline compared to testing individual genes.

REFERENCES: 1. Hicks JK, et al. *Clin Pharmacol Ther.* 2015;98(2), 127-134 2. Greden JF, et al. *J Psychiatr Res.* 2019; 111, 59-67