A 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 (GDI) 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 **G**enomics **U**sed to **I**mprove **DE**pression **D**ecisions (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 GDI (no, moderate, or significant) 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 for ***CYP2C19*** as defined by both CPIC and the combinatorial PGx test
  - Individual gene phenotypes for ***CYP2B6*** and *CYP3A4* as defined by the combinatorial PGx test
  - **Combinatorial PGx** combined phenotype
- All data were analyzed using ANCOVA tests with log-transformed lean body weight as a covariate.

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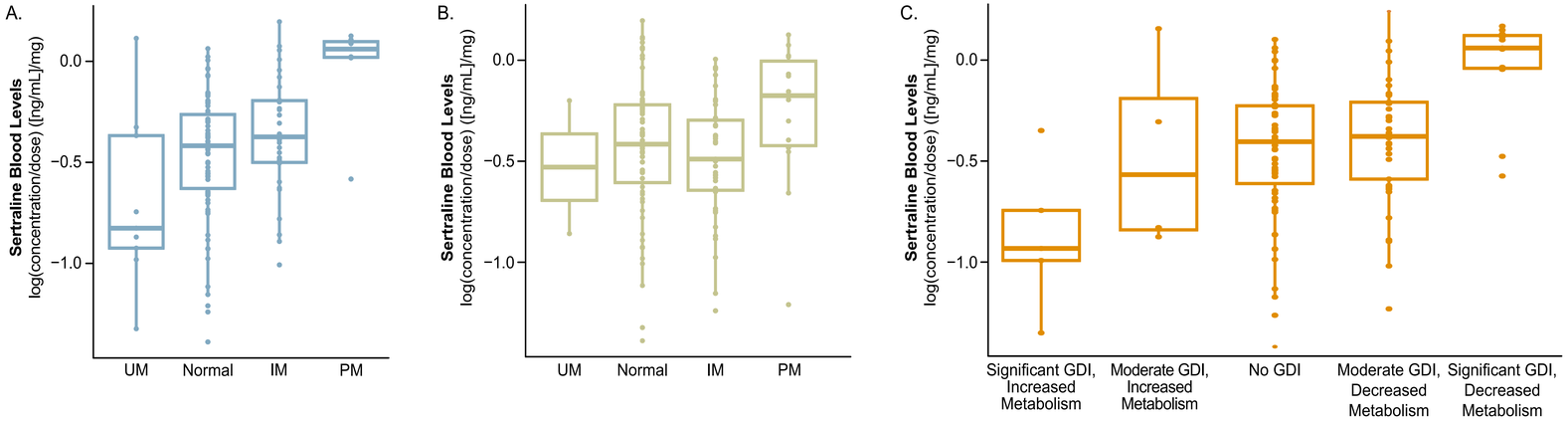
Figure 1. Sertraline blood levels across phenotypes for individual genes and the combinatorial PGx test.

Boxplots of the log-transformed concentration/dose ratios according to (A) individual ***CYP2C19*** phenotypes as determined by the combinatorial PGx test, (B) individual ***CYP2B6*** phenotypes as determined by the combinatorial PGx test, 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.



CYP2C19 Phenotypes

	UM	Normal	IM	PM
N	9	78	30	7
% Difference	-44%	*Ref*	21%	171%
p-value	0.02	*Ref*	0.19	0.0004

CYP2B6 Phenotypes

	UM	Normal	IM	PM
N	2	67	41	14
% Difference	-26%	*Ref*	-3%	54%
p-value	n/a	*Ref*	0.89	0.04

Combinatorial Pharmacogenomic Test Report Category

	Significant GDI, Increased Metabolism	Moderate GDI, Increased Metabolism	No GDI	Moderate GDI, Decreased Metabolism	Significant GDI, Decreased Metabolism
N	5	4	67	37	11
% Difference	-64%	9%	*Ref*	12%	161%
p-value	0.001	n/a	*Ref*	0.46	$2.7x10^{-5}$

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

- Individual gene phenotypes for *CYP2C19* as determined by CPIC (data not shown) and ***CYP2C19*** as determined by the combinatorial PGx test (Figure 1A) predicted blood levels with clinically meaningful differences for poor metabolizers.
- Individual gene phenotypes for ***CYP2B6*** as determined by the combinatorial PGx test (Figure 1B) predicted blood levels with clinically meaningful differences for poor metabolizers.
- There were no differences observed in metabolizer status for *CYP3A4* (data not shown).
- 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.

	Individual Gene		Combinatorial PGx Test	
Variables included in Model	F Statistic	p-value	F Statistic	p-value
CYP2C19 and Combinatorial PGx*	0.005	0.95	18.3	$3.8x10^{-5}$
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.

*CPIC defenition
**Combinatorial PGx definition

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.[3]
- 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 **3.** Shelton RC, et al. *Psychiatry Res.* 2020; 290: 113017