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 as 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.

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.

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

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<th>Combinatorial Pharmacogenomic Test Report Category</th>
<th>Significant GDI, Increased Metabolism</th>
<th>Moderate GDI, Increased Metabolism</th>
<th>No GDI</th>
<th>Moderate GDI, Decreased Metabolism</th>
<th>Significant GDI, Decreased Metabolism</th>
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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.

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.