Combinatorial Pharmacogenomic Testing Outperforms Individual Pharmacokinetic Gene Guidelines When Predicting Blood Levels of Psychotropic Medications and Clinical Outcomes in Patients with Depression

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BACKGROUND

- There are many available options for pharmacogenomic testing, and it is important that tests be rigorously evaluated to ensure appropriate clinical use and patient management.
- We evaluated the clinical validity of a combinatorial pharmacogenomic test and single-gene Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines against patient outcomes and medication blood levels to assess their ability to appropriately inform prescribing in major depressive disorder (MDD).

METHODS

- All patients were enrolled in the Genomics Used to Improve DEpression Decisions (GUIDED) randomized-controlled trial, had a diagnosis of MDD, and ≥1 prior medication failure.[1]
- All analyses were performed for all eligible medications (i.e. included on the combinatorial pharmacogenomic test report) and the subset of medications with CPIC level A or B evidence.
- The ability to predict **patient outcomes** at week 8 was assessed according to medication congruence with the combinatorial pharmacogenomic test or single-gene guideline recommendations.

	Congruent	Incongruent
Combinatorial Pharmacogenomic Test	• No or moderate gene-drug interactions.	• Significant gene-drug interactions
Single-Gene CPIC Guidelines*	• No actionable therapeutic recommendations for medication based on single-gene phenotype • No guidelines available for medication	• Actionable therapeutic recommendations (i.e. select an alternative drug or reduce dose by 50%) for medication based on single-gene phenotype

*Guidelines with Level A or Level B evidence (i.e. prescribing action recommended by CPIC) were considered. This includes guidelines amitriptyline, citalopram, desipramine, doxepin, escitalopram, fluvoxamine, imipramine, nortriptyline, paroxetine, sertraline.

- The ability to predict **medication blood levels** was evaluated according to predicted changes in metabolism.

	Significant Increase in Metablosim	No or Moderate in Metabolism	Significant Decrease in Metabolism
Combinatorial Pharmacogenomic Test	• Significant gene-drug interactions with increased metabolism	• No or moderate gene-drug interactions	• Significant gene-drug interactions with decreased metabolism
Single-Gene CPIC Guidelines	• Select an alternative drug based on ultrarapid metabolizer phenotype in the gene of interest[3]	• Initiate therapy with recommended starting dose • No recommendation due to lack of evidence • Reduce starting dose by 25%	• Reduce starting dose by 50% or select an alternative drug based on poor metabolizer phenotype in the gene of interest

	Combinatorial Pharmacogenomic Test		Single-Gene Guidelines	
Outcome	F-Statistic or X^2	P-Value	F-Statistic or X^2	P-Value
Patients Taking Any Medication on the Combinatorial Pharmacogenomic Test Report (N=1022)				
Symptom Improvement	9.4	0.002	0.15	0.695
Response	4.5	0.034	0.099	0.754
Remission	5.0	0.026	0.004	0.947
Patient Taking Medications with Single-Gene CPIC Guidelines (N=584)				
Symptom Improvement	7.9	0.005	0.38	0.539
Response	4.2	0.041	0.35	0.556
Remission	4.1	0.044	0.004	0.947

- There was a significant correlation between patient outcomes at week 8 and medication congruence with the combinatorial pharmacogenomic test, but not with congruence with single-gene CPIC guidelines (data not shown).
- In multivariate analysis that included both the combinatorial pharmacogenomic test and single-gene guidelines (see Table), the combinatorial pharmacogenomic test was the only significant predictor of patient outcomes.

- Both the combinatorial pharmacogenomic test and single-gene guidelines were significant predictors of blood levels when evaluated individually (individual models in Table).
- Only the combinatorial pharmacogenomic test remained significant when both were included in the multivariate model (combined models in Table).

	Combinatorial Pharmacogenomic Test		Single-Gene Guidelines	
Model	F-Statistic	P-Value	F-Statistic	P-Value
Blood Levels for Patients Taking Any Medication on the Combinatorial Pharmacogenomic Test Report (N=1,034)				
Individual Models	29.3	$7.55x10^{-8}$	6.7	0.010
Combined Model	25.0	$6.71x10^{-7}$	2.5	0.116
Blood Levels for Patients Taking Medictions with Single-Gene Guidelines (N=372)				
Individual Models	31.4	$4.06x10^{-8}$	9.9	0.002
Combined Model	22.8	$2.64x10^{-6}$	1.7	0.190

CONCLUSION

- This study shows that only the combinatorial pharmacogenomic test was significantly associated with improved patient outcomes.
- In addition, the combinatorial pharmacogenomic test was a superior predictor of medication blood levels across a larger group of medications relative to guidelines focused on only *CYP2C19* and *CYP2D6.*

REFERENCES: 1. Greden, JF. et al., J Psych Res. 2019. 111, 59-67

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