Primary, Secondary, and Meta-Analyses in Pharmacogenomics Clinical Trials: Where is Truth?

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RATIONALE

- Pharmacogenomic testing is a data-driven approach to help guide treatment decisions for patients with major depressive disorder (MDD), especially those who have failed prior medication treatment(s).
- Although well-designed prospective studies provide a high level of evidence for the overall clinical utility of an intervention, important findings may be overlooked when solely considering the "primary" outcome.

OBJECTIVE

- This poster discusses the value of remission as a clinically-relevant, secondary outcome associated with pharmacogenomic testing in MDD.

RESULTS

Pharmacogenomic Testing Improves Remission In Two Large Randomized Controlled Trials (RCT)

- The two largest prospective RCTs assessing the clinical utility of pharmacogenomic-guided care versus treatment-as-usual (TAU) showed a significant improvement in remission (Figure 1), despite not achieving statistical significance for the primary outcome of symptom improvement.

Meta-Analysis Supports Significant Increase in Remission Rate with Combinatorial Pharmacogenomic-Guided Care

- In a meta-analysis of all four clinical trials assessing the clinical utility of the GeneSight combinatorial pharmacogenomic test, pharmacogenomic-guided care was associated with a 49% increase in remission rate compared to TAU (p=0.001; Figure 2).

Greater Improvement in Remission Rate Among Genetic Subgroup of Patients

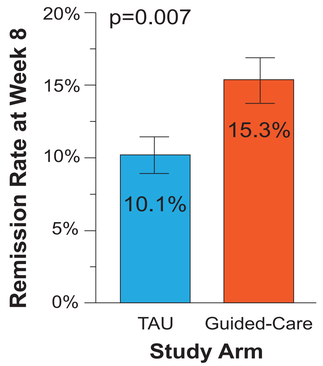
- Several noteworthy post-hoc analyses were conducted for the GUIDED trial (Greden et al. 2019), showing greater improvement in a subpopulation of patients taking medications with predicted gene-drug interactions.

Figure 1. Remission Rate in Two Large RCTs Assessing the Clinical Utility of Pharmacogenomic-Guided Care.

Remission was defined as HAM-D17 ≤7 in both trials

Greden et al. 2019

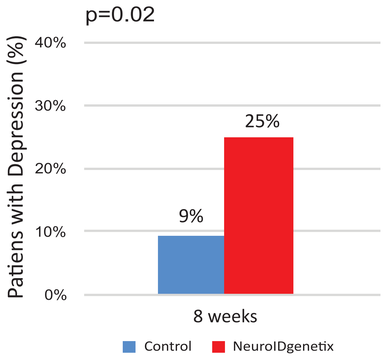
GeneSight Guided-Care vs TAU in per-protocol cohort (N=1,167)



Greden JF, et al. *J. Psychiatr. Res.* 2019; 111, 59–67

Bradley et al. 2018

NeuroIDgenetix Guided-Care vs TAU in subset of patients with severe depression (N=93)

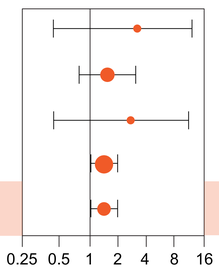


Bradley P, et al. *J. Psychiatr. Res.* 2018; 96, 100-107

Figure 2. Forest Plot of Fixed-Effects Meta-Analysis for Open-Label Trials and RCTs Assessing the Clinical Utility of Combinatorial Pharmacogenomic-Guided Care.

The relative risk ratio for remission between guided and unguided (TAU) care are shown.

Study	Guided-Care	TAU	RR [95% CI]	p-value	Weight
Hall-Flavin et al. 2012	22	22	2.00 [0.41, 9.79]	0.392	2.2%
Hall-Flavin et al. 2013	72	93	1.42 [0.84, 2.40]	0.189	20.6%
Winner et al. 2013	25	24	2.40 [0.51, 11.25]	0.267	2.4%
Greden et al. 2019	621	677	1.47 [1.12, 1.93]	0.006	74.8%
Random effects model	740	816	1.49 [1.17, 1.89]	0.001	100.0%



Heterogeneity:
$Q=0.54$, $I^2=0.00$, p=0.910

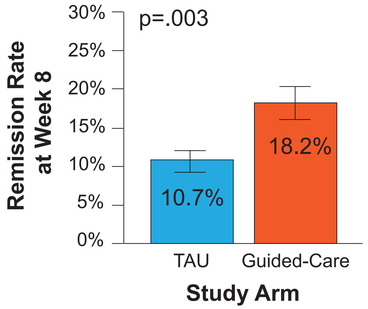
Brown L, et al. *Pharmacogenomics*. 2020; 21(8):559-569.

Studies included in meta-analysis:

Open Label Trials: Hall-Flavin DK, et al. *Transl. Psychiatry*. 2012; 2, e172. Hall-Flavin DK, et al. *Pharmacogenet. Genomics*. 2013; 23(10), 535–548. RCTs: Winner JG, et al. *Discov. Med*. 2013; 16(89), 219–227. Greden JF, et al. *J. Psychiatr. Res*. 2019; 111, 59–67.

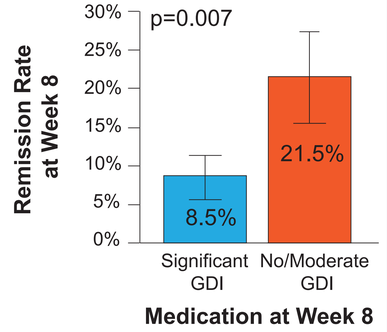
Figure 3. Remission Rate in Two Subpopulations Based on Medication Gene-Drug Interactions (GDI).

The rate of remission was higher in the guided-care arm versus TAU in the **subset of patients taking ≥1 medication subject to moderate or significant GDI at baseline**.



Thase ME, et al. *J. Clin. Psychiatr.* 2019; 80, 19m12910

Among **patients taking ≥1 medication subject to significant GDI at baseline**, the rate of remission was higher for patients who were taking only medications subject to no/moderate GDI at week 8.



Greden JF, et al. *J. Psychiatr. Res*. 2019; 111, 59–67

CONCLUSIONS

- Remission, the goal of MDD treatment, was a significant secondary outcome in randomized-controlled trials assessing the clinical utility of pharmacogenomic testing for MDD.
- Insights gained from primary, secondary and post-hoc outcomes, in addition to meta-analyses, are valuable in informing the overall clinical utility of pharmacogenomic testing, as well as shaping the design of future studies to meet and exceed precision health evidence thresholds for desired outcomes.

Future Considerations

- How should the field proceed if secondary outcomes are positive, but the primary outcome is negative in a pharmacogenomics randomized controlled trial?
- Can we consider multiple forms of evidence, and can meta-analyses of secondary outcomes be legitimate?

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