An Updated Meta-Analysis of the Clinical Utility of Combinatorial Pharmacogenomic Testing for Adult Patients with Depression

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Background

- Combinatorial pharmacogenomic (PGx) testing may be a valuable tool to improve clinical outcomes for patients with major depressive disorder (MDD) who have failed at least one treatment.
- An updated meta-analysis was conducted on prospective studies utilizing a commercially available combinatorial PGx test to compare PGx-guided care to unguided care in adult patients with MDD.

Design

- This updated meta-analysis builds upon Brown et al. 2020 (PMID: 32301649), which included 1,556 patients from 4 combinatorial studies.
- Brown et al. demonstrated that care guided by combinatorial PGx testing significantly improved outcomes for patients with MDD compared to unguided care.
  - **Symptom Improvement**: Δ=10.08%, 95% CI: 1.67–18.50, p=0.019
  - **Response:** Risk Ratio (RR)=1.40, 95% CI: 1.17–1.67, p<0.001
  - **Remission:** RR=1.49, 95% CI: 1.17–1.89, p=0.001
- In the current study, additional studies were identified using PRISMA guidelines and updated inclusion criteria to include additional depression scales.
  - Only studies using a specific combinatorial PGx test were included.
  - Additionally, only two-arm prospective studies evaluating symptom improvement, response, and/or remission using HAM-D17 or PHQ-9 in patients ≥18 years of age with MDD were included.
- A random-effects model was used to calculate the pooled relative RR of response and remission across all included studies and a subset of randomized controlled trials. A random-effects model was used in this subset because these studies use different depression scales.

Results

Table 1. Summary of Studies Evaluating the Combinatorial PGx Test in Adults with MDD

Study	Study Design	Sample Size	Depression Scale
Greden et al. 2019 PMID: 30677646	- 8-week, patient- and rater-blinded, randomized, controlled trial; open-label extension through 24 weeks. - **Two arms**: guided vs unguided - **Assessment points**: blinded: baseline, week 4, week 8; unblinded: week 12, week 24	1,541 (baseline*) 1,299** (completed week 8*)	HAM-D17
Hall-Flavin et al. 2012 PMID: 23047243	- 8-week, open-label study - **Two arms**: guided vs unguided - **Assessment points**: baseline, week 2, week 4, and week 8	51 (baseline) 44 (analyzed)	HAM-D17
Hall-Flavin et al. 2013 PMID: 24018772	- 8-week, open-label study - **Two arms**: guided vs unguided - **Assessment points**: baseline, week 2, week 4, and week 8	227 (baseline) 165 (completed week 8)	HAM-D17
Oslin et al. 2022 PMID: 35819423	- 24-week, pragmatic, patient- and clinician-unblinded, randomized controlled trial; follow-up for unguided at 36 weeks (after receiving results at 24 weeks) - **Two arms**: guided vs unguided - **Assessment points**: baseline, week 4, week 8, week 12, week 18, week 24, week 36 (unguided only)	1,944 (randomized) 1,668 (completed week 8) 1,541 (completed week 24)	PHQ-9
Tiwari et al. 2022 PMID: 35288545	- 8-week, patient- and rater-blinded, randomized, controlled trial; open-label extension though 52 weeks. - **Three arms**: guided vs e-guided (report +6 additional genes) vs unguided; Final analysis done with guided + e-guided vs unguided - **Assessment points**: blinded: baseline, week 4, week 8, week 12, week 24, week 36; unblinded: week 52	371 (baseline*) 308 (completed week 8*)	HAM-D17
Winner et al. 2013 PMID: 24229738	- 10-week, patient- and rater-blinded, randomized, controlled trial - **Two arms**: guided vs unguided - **Assessment points**: baseline, week 4, week 6, and week 10	51 (baseline) 49 (completed week 8)	HAM-D17

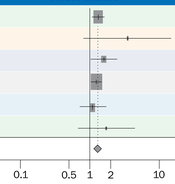
*Intent-to-treat cohort
**One patient was missing week 8 data

Figure 1. All Prospective Studies: Forest plot of 6 prospective studies meta-analyzed for response (A) and remission (B) using random-effects model to assess clinical utility of combinatorial PGx testing for adult patients with MDD.

A. Response

Study	logRR	SE(logRR)	Risk Ratio	RR	95%-CI	Weight
Greden 2019	0.2776	0.1019		1.32	[1.08; 1.61]	35.7%
Hall Flavin 2012	1.2528	0.7410		3.50	[0.82; 15.0]	0.7%
Hall Flavin 2013	0.4700	0.2196		1.60	[1.04; 2.46]	7.7%
Oslin 2022	0.2240	0.0890		1.25	[1.05; 1.49]	46.8%
Tiwari 2022	0.1021	0.2220		1.11	[0.72; 1.71]	7.5%
Winner 2013	0.5481	0.4769		1.73	[0.68; 4.41]	1.6%
Random-effects model				1.30	[1.16; 1.47]	100.0%

Heterogeneity: I^2=0%, τ^2<0.0001, p=0.58
Random-effects model: p<0.001



B. Remission

Study	logRR	SE(logRR)	Risk Ratio	RR	95%-CI	Weight
Greden 2019	0.3853	0.1388		1.47	[1.12; 1.93]	36.9%
Hall Flavin 2012	0.6931	0.8094		2.00	[0.41; 9.77]	1.1%
Hall Flavin 2013	0.3507	0.2678		1.42	[0.84; 2.40]	9.9%
Oslin 2022	0.2611	0.1280		1.30	[1.01; 1.67]	43.3%
Tiwari 2022	0.4515	0.3044		1.57	[0.86; 2.85]	7.7%
Winner 2013	0.8755	0.7892		2.40	[0.51; 11.3]	1.1%
Random-effects model				1.41	[1.19; 1.66]	100.0%

Heterogeneity: I^2=0%, τ^2=0, p=0.94
Random-effects model: p<0.001

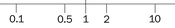
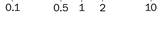


Figure 2. Randomized Controlled Trials: Forest plot of 4 prospective randomized controlled trials meta-analyzed for response (A) and remission (B) using random-effects model to assess clinical utility of combinatorial PGx testing for adult patients with MDD.

A. Response

Study	logRR	SE(logRR)	Risk Ratio	RR	95%-CI	Weight
Greden 2019	0.2776	0.1019		1.32	[1.08; 1.61]	39.0%
Oslin 2022	0.2240	0.0890		1.25	[1.05; 1.49]	51.1%
Tiwari 2022	0.1021	0.2220		1.11	[0.72; 1.71]	8.2%
Winner 2013	0.5481	0.4769		1.73	[0.68; 4.41]	1.8%
Random-effects model				1.27	[1.12; 1.44]	100.0%

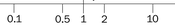
Heterogeneity: I^2=0%, τ^2=0, p=0.81
Random-effects model: p<0.001



B. Remission

Study	logRR	SE(logRR)	Risk Ratio	RR	95%-CI	Weight
Greden 2019	0.3853	0.1388		1.47	[1.12; 1.93]	41.4%
Oslin 2022	0.2611	0.1280		1.30	[1.01; 1.67]	48.7%
Tiwari 2022	0.4515	0.3044		1.57	[0.86; 2.85]	8.6%
Winner 2013	0.8755	0.7892		2.40	[0.51; 11.3]	1.3%
Random-effects model				1.40	[1.18; 1.67]	100.0%

Heterogeneity: I^2=0%, τ^2=0, p=0.78
Random-effects model: p<0.001



- Overall, 3,532 patients were included from six studies, with outcomes evaluated at week 8 or week 10 (Table 1). These studies were in patients who exeperienced at least one prior treatment failure.
- Clinical outcomes were significantly improved for patients with MDD whose care was guided by the combinatorial PGx test results compared to unguided care (Figure 1: response RR=1.30, 95% CI: 1.16–1.47, p<0.001; remission RR=1.41, 95% CI: 1.19–1.66, p<0.001).
- When the four randomized controlled trials were meta-analyzed, patients with MDD had significantly improved outcomes when care was guided by the combinatorial PGx test results compared to unguided care (Figure 2: response RR=1.27, 95% CI: 1.12–1.44, p<0.001; remission RR=1.40, 95% CI: 1.18–1.67, p<0.001).
- The Oslin et al. 2022 study had a design that was different from the other studies, notably use of PHQ-9 instead of HAM-D17 depression scale. Excluding this study from the overall meta-analysis had similar results: response RR=1.35, 95% CI: 1.15–1.59, p<0.001; remission RR=1.50, 95% CI: 1.20–1.87, p<0.001.

Conclusions

- Access to a combinatorial PGx test improved response and remission rates among adult patients with MDD who experienced at least one prior treatment failure.
- These findings further demonstrate the clinical utility of combinatorial PGx testing for the treatment of MDD and suggest that health care providers may observe significantly increased response and remission rates when using combinatorial PGx testing to inform medication selection in patients with MDD and one treatment failure.