Clinical utility of combinatorial pharmacogenomic testing in depression: Canadian patient- and rater-blinded, randomized controlled trial and meta-analysis

**BACKGROUND**
- Combinatorial pharmacogenetic (PGx) testing, a tool used to help guide the pharmacological treatment of depression, is associated with improved remission rates among patients with depression who have failed ≥1 previous medication trial.1,2
- As combinatorial PGx is unique from other PGx testing approaches, its clinical utility has been assessed independently through clinical trials, including the large Genomics Used to Improve Depression Decisions (GUIDED) randomized controlled trial (N=1,167), which used the GeneSight combinatorial PGx test, and was conducted in the United States from 2014–2017.3
- In Canada, there is also evidence to support the clinical and economic utility of combinatorial PGx testing; however, a direct evaluation in an RCT has not been performed.4,5

**Objective**
We assessed the clinical utility of combinatorial PGx testing to guide depression treatment in a Canadian population through the Genomic Applications Partnership Program-Major Depressive Disorder (GAPP-MDD) randomized controlled trial (ClinicalTrials.gov: NCT02466477).

**METHODS**
- **Study Design:**
  - 52-week, three-arm, multi-centre, patient- and rater-blinded, randomized, controlled trial evaluating clinical outcomes among patients whose treatment was guided by combinatorial PGx testing (GeneSight® Psychotropic) compared to treatment as usual (TAU).
- **Patient Population:**
  - ≥18 years, diagnosed with MDD, had inadequate response to ≥1 psychotropic medication within current depressive episode.
- **Primary Patient Assessment:**
  -HAM-D17 at week 8, administered by blinded central rater in the per-protocol cohort
- **Patient Outcomes:**
  - Symptom improvement (primary) – mean % change in HAM-D17 from baseline to week 8
  - Response – ≥50% decrease in HAM-D17 at week 8
  - Remission – HAM-D17 score of ≤7 at week 8
- **Considering the similarities in study design between the GAPP-MDD and GUIDED RCTs, patient outcomes observed in the GAPP-MDD trial were compared to those observed in the GUIDED trial.**

**RESULTS**
- N=276 and N=371 patients, respectively were included in the Per-Protocol and Intent-to-Treat cohorts of this study.
- On average, patients had failed 3.57 previous medication trials, indicating this is a treatment-resistant depression population.
- Combinatorial PGx-guided care was associated with improvement in patient outcomes in both the GAPP-MDD (not statistically significant) and GUIDED RCTs (Fig 1).
- In the GAPP-MDD trial, combinatorial PGx-guided care resulted in an 88% relative increase in remission compared to TAU (Fig 1).
- We conducted a meta-analysis of patient outcomes from the 3 RCTs of combinatorial PGx testing (GAPP-MDD, GUIDED, and Pine Rest—a similar, smaller RCT) (Fig 2).

**CONCLUSIONS & IMPLICATIONS**
- Although underpowered to detect statistically significant differences in outcomes between arms, this study demonstrated a 1.9-fold improvement in remission rate associated with combinatorial PGx-guided treatment compared to TAU.
- The results from the GAPP-MDD trial, together with GUIDED, suggest that combinatorial PGx testing can be an additional tool to help guide the treatment of depression.

**REFERENCES:**
1. Altar et al. 2015 (PMID: 27600312) 2. Winner et al. 2013 (PMID: 24018772)
8. Winner et al. 2015 (PMID: 24292738)

---

Table 1. Per-Protocol cohort demographic characteristics at baseline.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>TAU (N=246)</th>
<th>PGx-Guided Care (N=307)</th>
<th>Total (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>42.89 (14.16)</td>
<td>40.51 (14.11)</td>
<td>41.09 (14.12)</td>
</tr>
<tr>
<td>Gender, Female, n(%)</td>
<td>59 (63.4)</td>
<td>119 (65.0)</td>
<td>178 (64.5)</td>
</tr>
<tr>
<td>Ethnicity, Caucasian, n(%)</td>
<td>83 (89.2)</td>
<td>149 (81.4)</td>
<td>232 (84.1)</td>
</tr>
<tr>
<td>Ethnicity, Other, n(%)</td>
<td>10 (10.5)</td>
<td>34 (18.6)</td>
<td>44 (15.9)</td>
</tr>
<tr>
<td>Moderate Depression (HAM-D17 14-18), n(%)</td>
<td>28 (30.1)</td>
<td>56 (30.6)</td>
<td>84 (30.4)</td>
</tr>
<tr>
<td>Severe Depression (HAM-D17 19-22), n(%)</td>
<td>25 (26.9)</td>
<td>51 (27.9)</td>
<td>76 (27.5)</td>
</tr>
<tr>
<td>Very Severe Depression (HAM-D17 &gt; 22), n(%)</td>
<td>40 (43.0)</td>
<td>76 (41.5)</td>
<td>116 (42.0)</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder Comorbidity, n(%)</td>
<td>35 (37.6)</td>
<td>84 (45.9)</td>
<td>119 (43.1)</td>
</tr>
<tr>
<td>HAM-D17 mean (SD)</td>
<td>21.43 (4.53)</td>
<td>21.40 (4.73)</td>
<td>21.41 (4.66)</td>
</tr>
<tr>
<td>Number of Failed Psychiatric Medications, mean (SD)</td>
<td>3.04 (2.17)</td>
<td>3.84 (2.69)</td>
<td>3.57 (2.55)</td>
</tr>
</tbody>
</table>

**Figure 1. Comparison of HAM-D17 clinical outcomes by treatment arm between the GAPP-MDD and GUIDED trials.**

**Figure 2. Forest plot of fixed-effect meta-analysis for three RCTs that examined the clinical utility of combinatorial PGx testing in patients with MDD. Odds ratios for remission between the guided-care and TAU arms are shown.**