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

Arun Tiwari1,2,3, Clementi Zai1,2,3, Daniel J. Mueller1,2,3, Paige Davies4, Nicole Bragazza1,2, Paul Traxler5, Jim Li6, Julie-Anne Tanner7, C. Anthony Altar3, Bryan Dechairo6, James L. Kennedy1,2,3

1. Department of Psychiatry, University of Toronto, Toronto, ON; 2. Centre for Addiction and Mental Health, Toronto, ON; 3. Canada 5 Institute of Mental Health, University of Toronto, ON; 4. Canadian 5 Myelin Research, Mississauga, ON; 5. University of British Columbia, Vancouver, BC; 6. Splice Therapeutics, Germantown, MD, USA; 7. Myriad Genetics, Salt Lake City, UT, USA

BACKGROUND
- Combinatorial pharmacogenomic (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.1–3
- As combinatorial PGx is unique from other PGx testing approaches, its clinical utility has been assessed independently through clinical trials, including the large Genomic Applications Partnership Program – Major Depressive Disorder (GAPP-MDD), 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, who 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
  - 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 supported a 1.9-fold improvement in remission rate associated with combinatorial PGx-guided treatment compared to TAU.
- A meta-analysis of remission in all 3 RCTs (GAPP-MDD, GUIDED, Pine Rest) made an OR of 1.69 (95%CI 1.23-2.32, p=0.001), indicating that combinatorial PGx testing is associated with a 69% higher odds of achieving remission compared to TAU.
- Although underpowered to detect statistically significant differences in outcomes between arms, this study supported a 1.9-fold improvement in remission rate associated with combinatorial PGx-guided treatment compared to TAU.
- A meta-analysis of remission in all 3 RCTs (GAPP-MDD, GUIDED, Pine Rest) made an OR of 1.69 (95%CI 1.23-2.32, p=0.001), indicating that combinatorial PGx testing is associated with a 69% higher odds of achieving remission compared to TAU.

REFERENCES:
1. Altar et al. 2015 (PMID: 27603312) 2. Winner et al. 2013 (PMID: 24013772)
8. Winner et al. 2015 (PMID: 24292378)

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

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Treatment</th>
<th>Total (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>42.25 (14.16)</td>
<td>40.51 (14.11)</td>
</tr>
<tr>
<td>Gender, Female, n(%)</td>
<td>59 (63.4)</td>
<td>119 (66.9)</td>
</tr>
<tr>
<td>Ethnicity, Caucasian, n(%)</td>
<td>83 (89.2)</td>
<td>149 (84.1)</td>
</tr>
<tr>
<td>Ethnicity, Other, n(%)</td>
<td>10 (10.8)</td>
<td>34 (18.6)</td>
</tr>
<tr>
<td>Moderate Depression</td>
<td>28 (30.1)</td>
<td>56 (30.6)</td>
</tr>
<tr>
<td>Severe Depression</td>
<td>25 (26.9)</td>
<td>51 (27.9)</td>
</tr>
<tr>
<td>Very Severe Depression</td>
<td>40 (43.0)</td>
<td>76 (41.5)</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>35 (37.6)</td>
<td>64 (35.9)</td>
</tr>
<tr>
<td>Comorbidity, n(%)</td>
<td>35 (37.6)</td>
<td>84 (45.9)</td>
</tr>
<tr>
<td>Number of Failed Psychiatric Medications, mean (SD)</td>
<td>3.04 (2.17)</td>
<td>3.84 (2.69)</td>
</tr>
</tbody>
</table>

Table 2. Odds ratios for remission between the guided-care and TAU arms are shown.

Weighted Odds Ratio 95% CI p-value
TAU Guided-Care
GAPP-MDD | 0.131 [0.067; 0.256] 0.0000
GUIDED | 1.151 [0.599; 2.219] 0.686

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