

# Clinical utility of combinatorial pharmacogenetic testing in depression: Canadian patient- and rater-blinded, randomized, controlled trial

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## 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 trials.<sup>1</sup>
- 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.<sup>2</sup>
- In Canada, there is also evidence to support the clinical and economic utility of combinatorial PGx testing<sup>3,4,5,6</sup>; however, a direct evaluation in an RCT has not been performed.

## 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
- Patient Outcomes:
  - Symptom improvement – 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, and that the GAPP-MDD study ended early when power issues became apparent, patient outcomes observed in the GAPP-MDD trial were compared to those observed in the GUIDED trial.**  
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## 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).
- There was an increase in genetically-congruent medication prescribing in the combinatorial PGx guided-care arm relative to TAU (Fig 2)

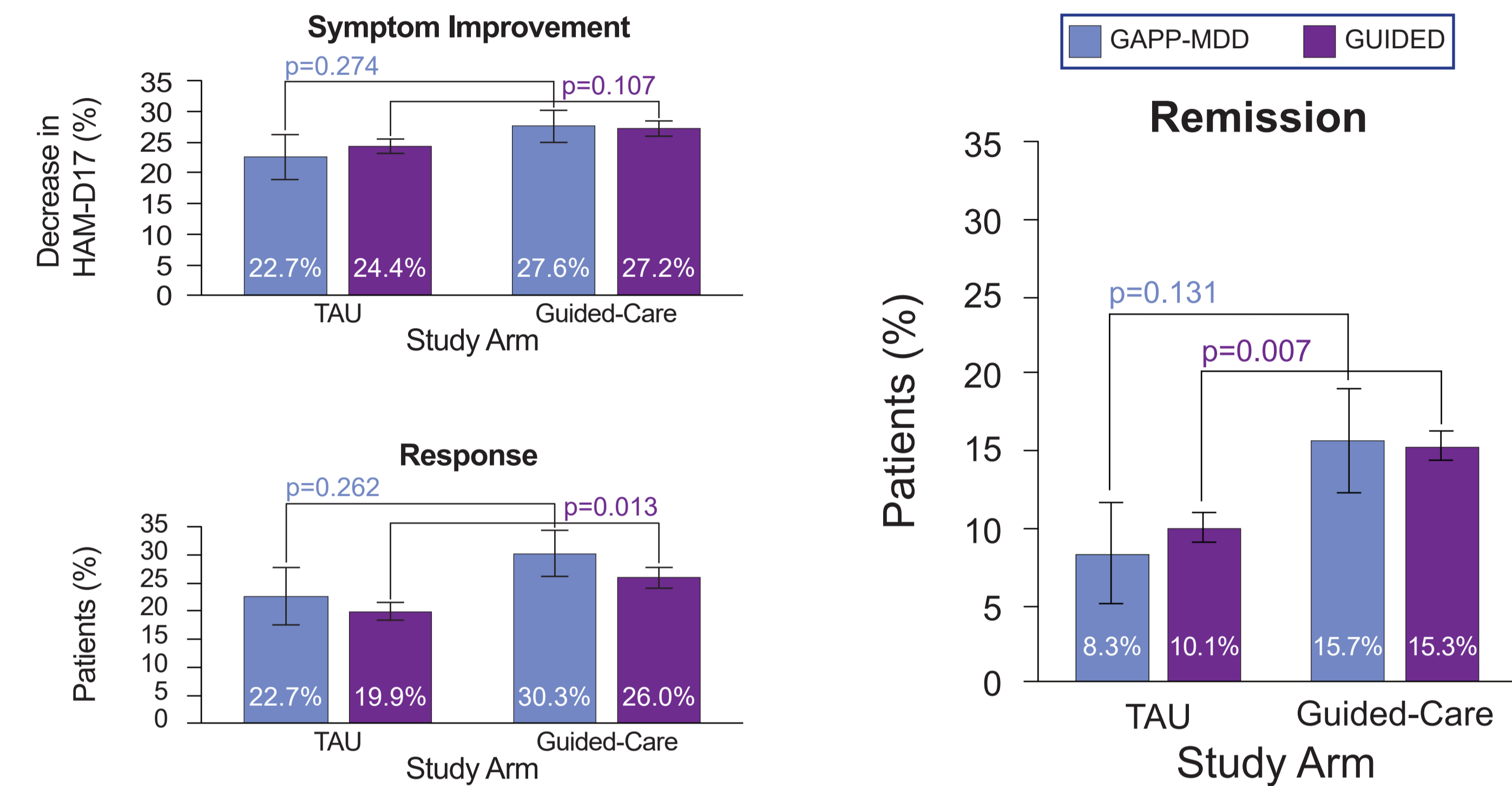
**Table 1. Demographic characteristics at baseline by treatment**

Demographics	Treatment		Total (N=276)
	TAU (N=93)	PGx-Guided Care (N=183)	
Age, mean (SD)	42.25 (14.16)	40.51 (14.11)	41.09 (14.12)
Gender, Female, n (%)	59 (63.4)	119 (65.0)	178 (64.5)
Ethnicity, Caucasian, n (%)	83 (89.2)	149 (81.4)	232 (84.1)
Ethnicity, Other, n (%)	10 (10.8)	34 (18.6)	44 (15.9)
Moderate Depression (HAM-D17 14-18), n (%)	28 (30.1)	56 (30.6)	84 (30.4)
Severe Depression (HAM-D17 19-22), n (%)	25 (26.9)	51 (27.9)	76 (27.5)
Very Severe Depression (HAM-D17 > 22), n (%)	40 (43.0)	76 (41.5)	116 (42.0)
Generalized Anxiety Disorder Comorbidity, n (%)	35 (37.6)	84 (45.9)	119 (43.1)
HAM-D17 mean (SD)	21.43 (4.53)	21.40 (4.73)	21.41 (4.66)
Number of Failed Psychiatric Medications, mean (SD)	3.04 (2.17)	3.84 (2.69)	3.57 (2.55)

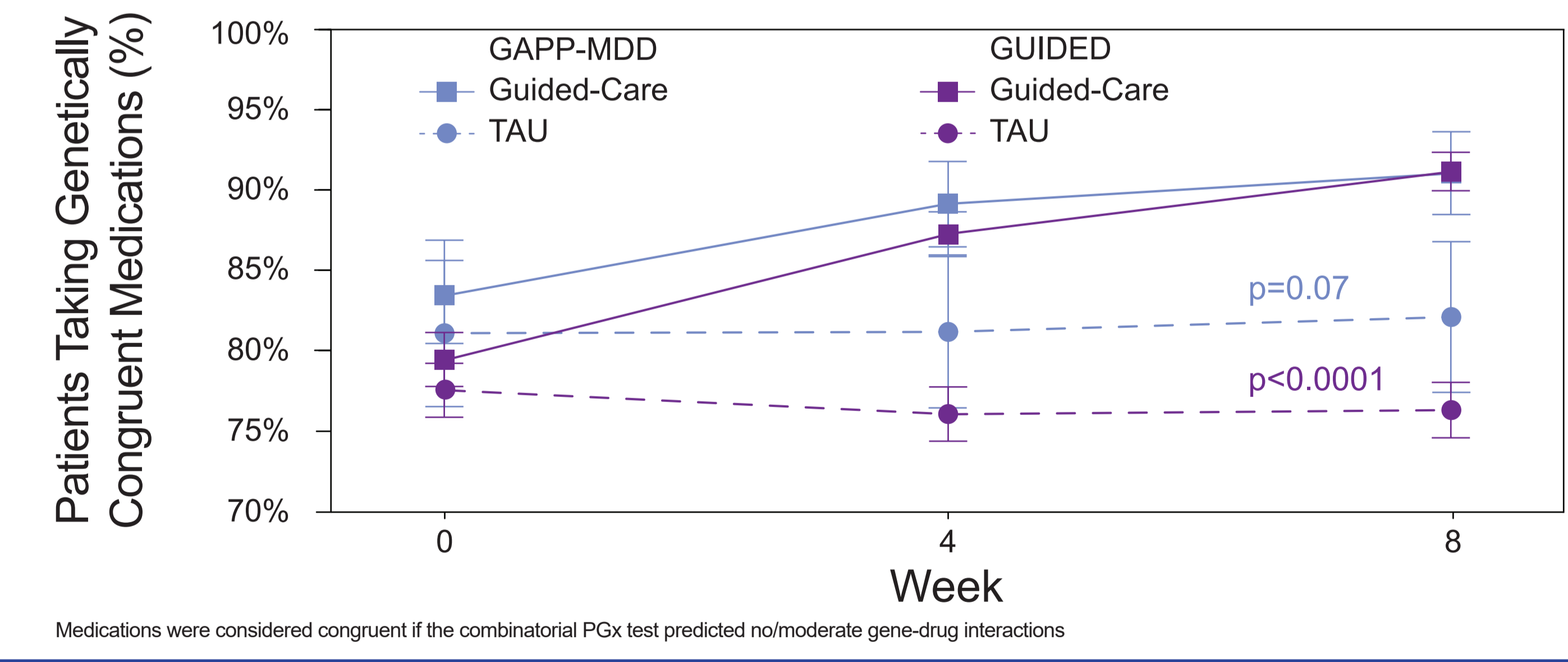
## CONCLUSIONS & IMPLICATIONS

- 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.
- Combinatorial PGx-guided treatment resulted in positive decision impact for prescribing clinicians, where the proportion of patients taking congruent medications increased to >90% in the PGx guided-care arm, with no change in the TAU arm.

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



**Figure 2. Comparison of medication congruency by week in the GAPP-MDD and GUIDED clinical trials**



- 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.

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