Galaxy Publication

Long-Term Impact of Pharmacogenomic Testing on Achieving Initial Remission and Treatment Response in Individuals with Major Depressive Disorder

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ABSTRACT

Patients with major depressive disorder (MDD) often face prolonged periods before achieving remission or a noticeable treatment response due to the trial-and-error nature of prescribing effective medications. Pharmacogenomic testing, which tailors drug selection based on genetic profiles, has demonstrated improvements in remission and response rates, yet its long-term effects remain unclear. This study aimed to investigate whether pharmacogenomic-guided therapy enhances remission and response over time in MDD patients and whether these benefits are sustained. This research involved a prespecified post hoc analysis of the PRIME Care (Precision Medicine in Mental Healthcare) randomized clinical trial, a pragmatic study comparing pharmacogenomic-guided therapy with standard care among veterans diagnosed with depression. Participants were enrolled across 22 Department of Veterans Affairs medical centers by 676 clinicians and randomized to either the pharmacogenomic-guided treatment group or usual care. Multivariate Cox proportional hazards models were applied to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) to assess the association between treatment approach and the first occurrence of response or remission as measured by the Patient Health Questionnaire-9 (PHQ-9). Of the 1,944 veterans in the PRIME Care trial, 1,764 (90.7%) had adequate follow-up data for analysis. Those receiving pharmacogenomic-guided therapy showed higher rates of remission (HR [95% CI] = 1.27 [1.05, 1.53]; p = 0.015) and response (HR [95% CI] = 1.21 [1.05, 1.40]; p = 0.010) compared to usual care. Analysis of Schoenfeld residuals revealed no significant changes in proportional hazards for remission (p = 0.931) or response (p = 0.112), indicating that the treatment benefit remained stable over the 24-week observation period. Use of pharmacogenomic-guided treatment led to quicker initial remission and response in patients with MDD, with these advantages persisting over six months and showing no evidence of diminishing over time.

Keywords: Pharmacogenomics, Pharmacogenetics, Antidepressive agents, Drug response, Depression, Precision medicine

Introduction

Major depressive disorder (MDD) is a prevalent and disabling psychiatric condition, affecting roughly one in five people in the United States over their lifetime and around 4% globally [1, 2]. Standard treatment relies on antidepressant medications, yet achieving meaningful symptom relief or full remission remains challenging. Fewer than 40% of patients reach remission with their first prescribed antidepressant, and the likelihood of success declines with each subsequent medication trial [3]. Because antidepressants may require several weeks to exert therapeutic effects [4, 5], patients often undergo multiple treatment attempts over extended periods. Data indicate that approximately 50% of patients try two or more different antidepressants within three years of diagnosis, while about one-third try three or more, prolonging symptom burden and increasing healthcare costs [6, 7]. Pharmacogenomic (PGx) testing offers a strategy to guide antidepressant selection by analyzing genetic variations that influence drug metabolism and response, potentially reducing adverse effects or suboptimal dosing [8]. Clinical guidelines provide recommendations for incorporating PGx results into antidepressant prescribing [9-12],

and the FDA includes PGx information in labeling for many antidepressants [13]. Evidence from randomized trials demonstrates that PGx-guided treatment can improve remission rates compared with usual care [14, 15]. A meta-analysis of thirteen trials encompassing 4,767 patients reported a 41% higher likelihood of remission with PGx-informed therapy [16], with subsequent meta-analyses confirming these findings [17-22].

Despite these benefits, limited data exist regarding the effect of PGx-guided therapy on the timing of remission and response, as well as whether these effects persist. In the GUIDED trial, the probability of remission in the PGx-guided arm doubled from week 8 to week 24, suggesting sustained benefit, but comparisons to the control group were unavailable after week 8 because clinicians could access PGx results for all participants [14].

The PRIME Care trial, the largest PGx study to date in MDD, enrolled 1,944 veterans and compared outcomes between PGx-guided therapy and standard care over 24 weeks [15]. PRIME Care collected more frequent outcome data than previous trials (at weeks 4, 8, 12, 18, and 24) and demonstrated that PGx-guided patients were less likely to be prescribed medications with significant gene-drug interactions and were 28% more likely to achieve remission across the trial duration. Early time points (weeks 8 and 12) showed significantly higher remission in the PGx-guided arm, though differences at weeks 18 and 24 were not statistically significant. While the original analysis suggested the effect of PGx testing may not persist, this conclusion was not directly tested. The present study specifically evaluates whether PGx-guided therapy produces lasting improvements in remission and response by analyzing time-to-event outcomes in the PRIME Care cohort.

Materials and Methods

Study design and participants

This investigation is a post hoc analysis of the PRIME Care trial, following a prespecified analysis plan. PRIME Care was a pragmatic, randomized trial enrolling patients with MDD who had experienced at least one prior treatment failure. Participants were randomized to receive either PGx-guided therapy or usual care for 24 weeks at the start of a new antidepressant treatment episode. Baseline assessments occurred before randomization, with follow-up visits scheduled at weeks 4, 8, 12, 18, and 24. Detailed trial eligibility criteria have been reported previously [15, 23]. The post hoc study was reviewed and deemed exempt by the Advarra Institutional Review Board under 45 CFR 46.104(d)(4).

Collected variables included demographic and clinical information: age, race (Black/African American, White, Other/unspecified), Hispanic ethnicity, sex, smoking history (cigarettes per day over the past 30 days), previous psychotropic treatments, days since randomization, and care setting (primary care, mental health, or integrated care) **(Table 1).**

Table 1. Baseline patient characteristics.

Characteristic	Group, no. (%)		
	Pharmacogenomic-guided (N = 884)	Usual care (N = 880)	p-value[a]
Patient characteristics			
Age			0.918
60+	241 (27)	237 (27)	
<60	643 (73)	643 (73)	
Sex			0.110
Female	205 (23)	234 (27)	
Male	679 (77)	646 (73)	
Race			0.291
Black	170 (19)	152 (17)	
White	588 (67)	616 (70)	
Other/unspecified	126 (14)	112 (13)	
Ethnicity			0.638
Hispanic	104 (12)	92 (10)	

Non-Hispanic	777 (88)	784 (89)	
Unspecified	3 (0)	4 (0)	
Smoking status			0.857
Smoker	151 (17)	158 (18)	
Non-smoker	727 (82)	717 (81)	
Unspecified	6 (1)	5 (1)	
Clinical symptoms			
PHQ-9 score mean (SD)	17.5 (4.3)	17.4 (4.3)	0.756
Treatment refractory[b]	270 (31)	273 (31)	0.868
PTSD presence	517 (58)	506 (58)	0.776
Practice location			0.853
Integrated care	163 (18)	162 (18)	
Primary care	109 (12)	101 (11)	
Specialty mental health	612 (69)	617 (70)	

[a] Group differences were examined using chi-square tests for categorical measures, while baseline PHQ-9 scores were compared between arms using the Wilcoxon rank-sum test.

[b] Treatment-refractory depression was defined as a self-reported history of either two or more adequate antidepressant trials lasting at least six weeks at standard dosing, or prior treatment with electroconvulsive therapy or transcranial magnetic stimulation.

Clinical assessments and endpoints

For this analysis, clinical evaluations performed at baseline and at each scheduled follow-up visit included the Patient Health Questionnaire-9 (PHQ-9) [24] and the PTSD Checklist for DSM-5 (PCL-5) [25].

The main outcomes of interest were the time to the first occurrence of remission—defined as a PHQ-9 score of 5 or below—and the time to the first recorded treatment response, characterized by at least a 50% reduction from the individual's baseline PHQ-9 score. PHQ-9 values span a 0–27-point scale.

Statistical analysis

Baseline variables were contrasted between the PGx-guided and usual-care groups using chi-square tests for categorical measures and the Wilcoxon rank-sum test for initial PHQ-9 scores, applying a two-sided α threshold of 0.05.

The primary analytical approach employed two multivariable Cox proportional hazards models—one for remission and one for response—to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) describing the association between study arm assignment and the first observed remission or response [26]. The baseline PHQ-9 score served as the sole additional covariate. Tied event times were handled using the Efron approximation. Likelihood ratio testing was used to evaluate statistical significance for individual predictors.

Assumptions of proportional hazards for the treatment-arm variable were evaluated using Schoenfeld residuals. Because two main outcomes were tested, significance thresholds were adjusted via Bonferroni correction (α = 0.025). In accordance with the original PRIME Care protocol and timing of follow-up assessments, study week (4, 8, 12, 18, or 24) was used as the analysis time scale. Right-censoring occurred at the earliest instance of a missing follow-up PHQ-9 score or when a visit was recorded outside of the prespecified time windows: 14–42 days (week 4), 42–70 days (week 8), 70–105 days (week 12), 105–147 days (week 18), and 147–189 days (week 24). These windows were created post hoc based on midpoint intervals between scheduled visits. Participants whose data were fully censored after baseline were excluded.

Two sensitivity analyses were conducted: one omitting right-censoring based on visit date, and a second incorporating additional predefined covariates (age $\geq$60, race, Hispanic ethnicity, sex, baseline PTSD status, history of treatment-refractory depression, regular smoking defined as $\geq$1 cigarette per day in the prior 30 days, and clinic type).

All statistical procedures were carried out using R version 4.4.1 [27].

Results and Discussion

Baseline characteristics

Among the 1,944 PRIME Care participants, 180 individuals (9.3%) had only baseline information available after censoring and were excluded. The final analytic sample comprised 1,764 participants (90.7%), with 884 assigned to the PGx-guided arm and 880 to usual care. Most patients in both groups were younger than 60 (73% in each arm) and predominantly male (77% in the PGx-guided arm and 73% in usual care) (**Table 1**). The sample was largely White (67% PGx-guided, 70% usual care), non-Hispanic (88% and 89%, respectively), and non-smoking (82% and 81%). Average baseline PHQ-9 values reflected moderately severe depressive symptoms (17.5 and 17.4). Rates of treatment-refractory depression (31%) and comorbid PTSD (58%) were also similar across arms. Comparison of all baseline characteristics indicated no statistically meaningful differences between the treatment groups.

Time-to-event findings

Results from the Cox models and corresponding likelihood ratio tests demonstrated that PGx-guided therapy was associated with a higher probability of achieving both remission (HR = 1.27; 95% CI: 1.05–1.53; p = 0.015) and response (HR = 1.21; 95% CI: 1.05–1.40; p = 0.010) at any point during follow-up. Kaplan–Meier curves constructed using reported visit dates suggest that the PGx-guided group began showing higher cumulative remission and response rates early in the study, and these differences continued throughout the full observation period **(Figure 1).**

a)   b)
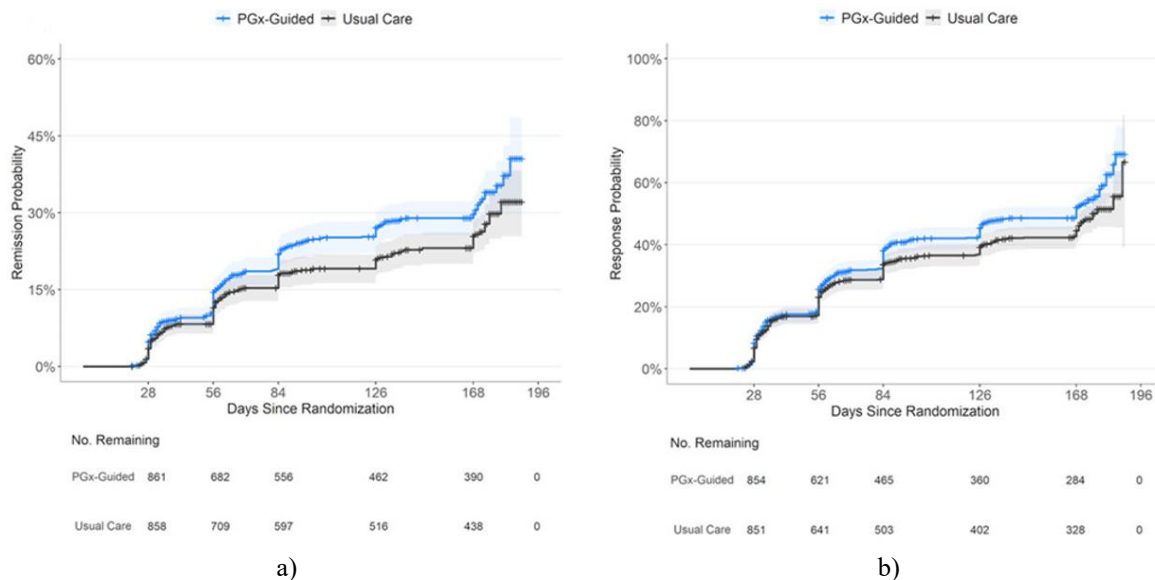
Figure 1. Cumulative Incidence of Remission and Response by Study Arm. The Kaplan–Meier estimates in panel a (remission) and panel b (response) illustrate how the likelihood of achieving each outcome progressed over time for participants treated with PGx-guided therapy compared with those receiving usual care, using the reported visit date—expressed as days from randomization—as the reference timescale for clearer visualization. The shaded bands represent the corresponding 95% confidence intervals, and the counts displayed beneath the x-axis reflect the number of patients in each arm who had not yet experienced the event. Cross-shaped tick marks on the curves denote censoring events. It should be noted that the main analysis relied on study week as the time variable, and comparisons between groups were not based on reported visit dates.

The Schoenfeld residuals test performed for the study arm covariate demonstrated no statistical significance for either remission (p = 0.931) or response (p = 0.112), indicating an absence of detectable time-varying effects and supporting the proportional-hazards assumption. Visual inspection of the Schoenfeld residual plots revealed no meaningful shifts in the hazard ratios for remission or response during the follow-up window **(Figure 2).** Collectively, these findings show that the advantage associated with PGx-guided treatment remained stable throughout the 24-week observation period.
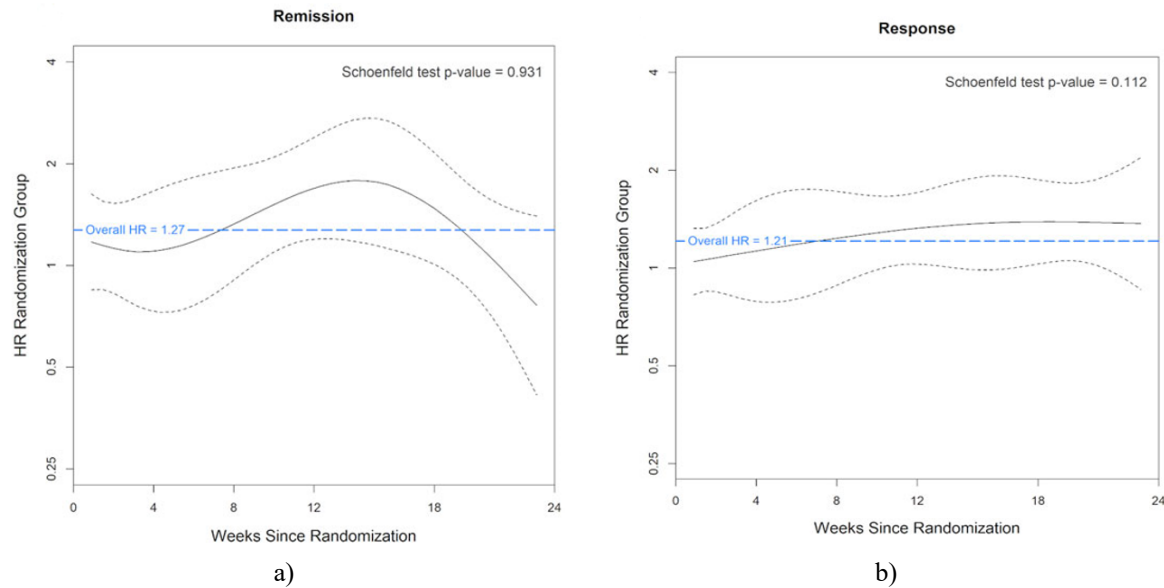
a)　　　　　　　　　　　　　　　　　　b)

Figure 2. Time-Varying Influence of Study Arm on Remission and Response Depicted on the Log Hazard Ratio Scale. Panels a and b display smoothed trajectories of the scaled Schoenfeld residuals that describe how the study arm influenced remission and response over study weeks. The horizontal blue dashed line marks the overall hazard ratio generated by the Cox model, while the surrounding black dashed lines denote the 95% confidence envelope for the estimated effect across time. A consistent departure of the smoothed line from this band would suggest a violation of the proportional hazards assumption.

Sensitivity analyses

To evaluate the robustness of the primary findings, the models were re-estimated after removing right-censoring based on reported visit dates. This approach reduced the number of excluded participants to 125 (6.4%), leaving 1,819 individuals (93.6%) eligible for analysis. In this sensitivity set, the associations between study assignment and time-to-remission (HR [95% CI] = 1.24 [1.03, 1.49]; p = 0.022) and time-to-response (HR [95% CI] = 1.20 [1.05, 1.38]; p = 0.010) remained closely aligned with the primary results. Likewise, the Schoenfeld residuals tests for remission (p = 0.699) and response (p = 0.227) mirrored those observed earlier, again yielding no evidence that the study arm effect changed with time.

A second set of models incorporated additional prespecified covariates, including age ≥60 years, race, Hispanic ethnicity, sex, baseline PTSD diagnosis, history of treatment-refractory depression, recent smoking (≥1 cigarette daily during the past 30 days), and clinical site. Even after adjusting for this expanded panel of variables, the associations between study arm and remission (HR [95% CI] = 1.30 [1.07, 1.57]; p = 0.008) or response (HR [95% CI] = 1.23 [1.07, 1.43]; p = 0.004) remained consistent with those seen in the primary analysis. Schoenfeld residuals again showed no significant violations of the proportional hazards assumption for remission (p = 0.990) or response (p = 0.092). Together, these sensitivity checks confirm that the primary findings were not meaningfully altered by changes in censoring strategy or model covariates.

This investigation is the first to demonstrate that PGx-guided prescribing for individuals with MDD not only improves the chances of achieving an initial remission or response but also maintains this advantage for up to six months following testing, with no indication that the effect diminishes over time. These results extend prior work documenting higher overall rates of remission and response with PGx-informed care compared to standard management [14-21].

Time-to-event modeling in the present study revealed that PGx-guided treatment corresponded to a 27% increase in the remission rate and a 21% increase in the response rate at any time during weeks 4–24 after randomization when compared with usual care. Notably, the original PRIME Care report did not detect significant differences in overall proportions of remitters at weeks 18 or 24 [22], but that analysis counted all remission and response episodes. In contrast, the current analysis focused solely on the first remission or response event post-randomization, meaning the earlier study may have included individuals who initially relapsed before achieving another remission or response. Relapse—defined as a recurrence of depressive symptoms—affects roughly 20% of patients within a year of remission [28], making relapse likely within the PRIME Care cohort.

The higher hazard of initial remission and response observed here indicates that PGx-guided treatment accelerated clinical improvement relative to usual care. These findings parallel a recent study showing that PGx-directed dosing of tricyclic antidepressants allowed patients to reach therapeutic serum levels more quickly than conventional dosing [29]. Faster remission may have lasting benefits: analyses from the STAR*D trial [3, 30] demonstrated that early remitters experienced lower relapse rates and endured longer relapse-free intervals compared to later remitters. Similarly, in another cohort, patients who responded or remitted within the first six treatment weeks were more likely to remain in remission one year later [31].

Additional clinical advantages may follow rapid symptom resolution. Quicker remission can decrease the likelihood of developing treatment-resistant depression [32, 33] and may lessen the burden of residual symptoms—including mood reactivity, sadness, and anhedonia. In a large sample of 1,595 individuals, those who remitted within 6–8 weeks had fewer and milder residual symptoms than those whose remission occurred after 16–20 weeks [34].

Faster achievement of remission or response may also carry important financial implications. In 2019, Major Depressive Disorder in the United States was estimated to impose an overall economic burden of $333.7 billion, spanning both direct medical expenditures and substantial work-related losses such as absenteeism, reduced productivity, and unemployment [35]. A modeling study showed that an intervention capable of accelerating time-to-response could translate into annual savings of roughly $25 billion [35]. Moreover, interventions that decrease relapse rates and lower the likelihood of treatment-resistant depression—benefits that often accompany quicker remission—are projected to further reduce healthcare expenditures [36-38].

The sustained advantage of PGx-guided treatment observed across the study period provides a possible explanation for emerging evidence that PGx-based prescribing can lower healthcare utilization, including reductions in psychiatric hospital admissions [39]. These patterns suggest that the influence of PGx testing may extend well beyond the 6-month horizon captured here. Achieving and maintaining remission is the central therapeutic objective for individuals with MDD [40], and the durability of PGx-guided antidepressant treatment may ultimately compare favorably with newer rapid-acting agents whose long-term stability remains uncertain [41].

Strengths and limitations

This investigation benefits from the design of the PRIME Care trial, which enrolled a large, diverse sample of individuals with depression and adopted a pragmatic framework intended to emulate everyday clinical settings [15]. The trial also followed a prespecified analytic structure and repeatedly assessed depressive symptoms across several scheduled visits within a 24-week interval. Unlike the original report, which examined outcomes at individual time points, the present analysis assessed the timing of initial improvement across the entire follow-up window. Additionally, whereas Oslin *et al.* (2022) [15] reported a non-significant arm-by-time interaction, this analysis applied time-to-event approaches that provide a more rigorous and clinically intuitive assessment of how PGx-guided treatment influences the trajectory of early improvement.

Nevertheless, certain constraints must be acknowledged. The PRIME Care protocol did not collect data beyond 24 weeks, preventing evaluation of whether the effect of PGx persists over longer periods. Only the first remission or response event was analyzed, meaning later improvements after relapse were not captured. The findings also pertain to one specific PGx test and may not generalize to all commercially available PGx tools. Finally, because the trial drew participants from a veteran population—with higher proportions of men and patients with PTSD than typically seen in broader MDD cohorts—the representativeness of these results for other patient groups remains uncertain.

Conclusion

Pharmacogenomic testing accelerated the attainment of initial remission and response among individuals with MDD, and this advantage remained stable throughout the 6-month follow-up period. Future research priorities include quantifying the economic implications of these enhanced clinical outcomes, determining how PGx testing influences relapse patterns, and examining other patient populations to evaluate the broader applicability of these findings.

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