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# Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder

## The PRIME Care Randomized Clinical Trial

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**IMPORTANCE** Selecting effective antidepressants for the treatment of major depressive disorder (MDD) is an imprecise practice, with remission rates of about 30% at the initial treatment.

**OBJECTIVE** To determine whether pharmacogenomic testing affects antidepressant medication selection and whether such testing leads to better clinical outcomes.

**DESIGN, SETTING, AND PARTICIPANTS** A pragmatic, randomized clinical trial that compared treatment guided by pharmacogenomic testing vs usual care. Participants included 676 clinicians and 1944 patients. Participants were enrolled from 22 Department of Veterans Affairs medical centers from July 2017 through February 2021, with follow-up ending November 2021. Eligible patients were those with MDD who were initiating or switching treatment with a single antidepressant. Exclusion criteria included an active substance use disorder, mania, psychosis, or concurrent treatment with a specified list of medications.

**INTERVENTIONS** Results from a commercial pharmacogenomic test were given to clinicians in the pharmacogenomic-guided group (n = 966). The comparison group received usual care and access to pharmacogenomic results after 24 weeks (n = 978).

**MAIN OUTCOMES AND MEASURES** The co–primary outcomes were the proportion of prescriptions with a predicted drug-gene interaction written in the 30 days after randomization and remission of depressive symptoms as measured by the Patient Health Questionnaire–9 (PHQ-9) (remission was defined as PHQ-9 $\leq$ 5). Remission was analyzed as a repeated measure across 24 weeks by blinded raters.

**RESULTS** Among 1944 patients who were randomized (mean age, 48 years; 491 women [25%]), 1541 (79%) completed the 24-week assessment. The estimated risks for receiving an antidepressant with none, moderate, and substantial drug-gene interactions for the pharmacogenomic-guided group were 59.3%, 30.0%, and 10.7% compared with 25.7%, 54.6%, and 19.7% in the usual care group. The pharmacogenomic-guided group was more likely to receive a medication with a lower potential drug-gene interaction for no drug-gene vs moderate/substantial interaction (odds ratio [OR], 4.32 [95% CI, 3.47 to 5.39]; $P < .001$) and no/moderate vs substantial interaction (OR, 2.08 [95% CI, 1.52 to 2.84]; $P = .005$) ($P < .001$ for overall comparison). Remission rates over 24 weeks were higher among patients whose care was guided by pharmacogenomic testing than those in usual care (OR, 1.28 [95% CI, 1.05 to 1.57]; $P = .02$; risk difference, 2.8% [95% CI, 0.6% to 5.1%]) but were not significantly higher at week 24 when 130 patients in the pharmacogenomic-guided group and 126 patients in the usual care group were in remission (estimated risk difference, 1.5% [95% CI, −2.4% to 5.3%]; $P = .45$).

**CONCLUSIONS AND RELEVANCE** Among patients with MDD, provision of pharmacogenomic testing for drug-gene interactions reduced prescription of medications with predicted drug-gene interactions compared with usual care. Provision of test results had small nonpersistent effects on symptom remission.

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Visual Abstract

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Supplemental content

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Pharmacogenomic testing is receiving increased attention as a mechanism to personalize medication selection. Despite the proliferation of pharmacogenomic testing, there is limited research demonstrating improved clinical outcomes. Currently, most pharmacogenomic testing focuses on variation in the genes that encode hepatic cytochrome P450 enzymes.[1] The test results classify how an individual metabolizes medications: poor, normal, intermediate, and rapid metabolizing.

In theory, pharmacogenomic testing may improve drug selection or dosing in patients with genetic variation that alters pharmacokinetics or pharmacodynamics. Pharmacogenomic testing may be particularly helpful in the treatment of major depressive disorder (MDD) where initial treatment response can be expected in 28% to 33% of patients, with the odds of remission and treatment engagement decreasing for each treatment trial.[2,3]

The Genomics Used to Improve Depression Decisions (GUIDED) Trial, which enrolled 1541 patients, compared usual care with treatment guided by pharmacogenomic testing. The results showed an association between pharmacogenomic-guided treatment and treatment outcomes.[4,5] Treatment outcome differences were small (5%-6%) and seen only in secondary outcomes. A systematic review of 4 small randomized clinical trials and 2 open-label trials provided modest evidence of an association between pharmacogenomic-guided treatment and both symptom response and symptom remission.[6]

The Precision Medicine in Mental Health Care (PRIME Care) Trial was designed to evaluate clinical outcomes related to pharmacogenomic testing in routine clinical practice. This study used a pragmatic study design to test 2 primary study hypotheses: (1) patients and clinicians would use pharmacogenomic test results to select fewer antidepressants with potential drug-gene interactions (treatment initiation) and (2) treatment in the pharmacogenomic-guided group would result in greater rates of remission.[7]

### Key Points

**Question** Does provision of pharmacogenomic testing for drug-gene interactions affect selection of antidepressant medication and response of depressive symptoms in patients with major depressive disorder (MDD)?

**Findings** In this randomized clinical trial that included 1944 patients with MDD, provision of pharmacogenomic tests for drug interactions compared with usual care resulted in prescriptions with no predicted drug-gene interactions in 45% vs 18%, respectively, a difference that was statistically significant. Remission of symptoms reached a maximum difference of 16.5% vs 11.2% at 12 weeks but was not significantly different at 24 weeks.

**Meaning** Pharmacogenomic testing for drug-gene interactions in MDD reduced prescription of medications with predicted drug-gene interactions but had small and nonpersistent effects on symptom remission.

## Methods

### Trial Design

This single-blind pragmatic trial was conducted at 22 Department of Veterans Affairs (VA) medical centers. An executive committee and an external advisory board oversaw the trial and regularly assessed safety. The trial protocol and all amendments were approved by the executive committee and the VA Central Institutional Review Board. Both clinicians and patients provided informed consent. The protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively.[7] Changes to the protocol included modifying the exclusion criteria (removing concurrent posttraumatic stress disorder [PTSD], adding prescriptions for addiction treatment), adding an assessment for suicidal risk, and converting to virtual consent and assessments during the COVID-19 pandemic. The change in statistical modeling from the original plan of using mixed-effects models is described in the eAppendix in Supplement 3.

### Participants

The study focused on enrolling clinicians in primary care (including integrated care programs) and mental health outpatient settings. Patients were identified by their treating clinician who established their eligibility. Those eligible were receiving care at VA medical centers, aged 18 to 80 years, with a diagnosis of MDD, a history of at least 1 treatment episode, and a plan to start a new episode of antidepressant monotherapy (either switching from a prior treatment or starting a new treatment episode). Exclusion criteria were an active substance use disorder; bipolar illness; psychosis; borderline or antisocial personality disorder; treatment with an antipsychotic medication, methadone, buprenorphine, or naltrexone; augmentation treatment; and lack of a bank account for payments. After consent, the baseline assessments were completed, including the Patient Health Questionnaire-9 (PHQ-9) to confirm depression severity inclusion criteria (required total score >9).[8] Patients were compensated for research assessments. Clinicians were not compensated for participation.

### Randomization

After DNA collection, patients were randomly assigned in a 1:1 ratio to receive pharmacogenomic test results when available, typically within 2 to 3 business days after randomization (pharmacogenomic-guided group) or 24 weeks later (usual care group) using random permuted blocks of sizes 4 and 6 and stratified by sites and clinicians (nested within sites). A centralized computer-generated system (DataFax 4.3 Clinical Data Management System) was used to provide randomization to sites.

### Interventions

As a pragmatic effectiveness study, all treatment decisions were made by the referring clinician and patient. Clinicians were directed to initiate treatment as usual, with patients assigned to the usual care group on the day of randomization. In the pharmacogenomic-guided group, clinicians were

asked to initiate treatment when the pharmacogenomic results were available for discussion with their patients. After randomization, subsequent changes in treatment were allowed as clinically indicated. Educational materials focusing on test interpretation, including consideration of medications with lower risk of drug-gene interactions, were provided. The pharmacogenomic testing was conducted by Myriad Genetics using its GeneSight panel, which uses a combinatorial interpretation of 4 pharmacodynamic gene variants and 8 pharmacokinetic gene variants (eTable 1 in Supplement 3).

## Assessments

Assessments included the PHQ-9 (range, 0-27 points; higher scores indicate worse symptoms)[8]; Generalized Anxiety Disorder-7 (range, 0-21 points; higher scores indicate worse symptoms)[9]; Columbia-Suicide Severity Rating Scale (6 yes/no questions, scored as no, low, moderate, or severe suicidal risk)[10]; Veterans RAND 12-item Health Survey (2 subscores; mental health [Mental Component Summary] and physical health [Physical Component Summary]; range, 0-100; higher scores indicate higher function)[11]; current alcohol use estimated using a 7-day timeline followback assessment[12]; a modified version of the National Institute on Drug Abuse's Alcohol, Smoking, and Substance Involvement Screening Test to measure substance use as present or absent in the last 30 days[13]; adverse drug reactions (headache, nausea, vomiting, sexual dysfunction, diarrhea, and constipation rated as none, mild, moderate, or interfering); and, for patients with trauma exposure, the PTSD Checklist for *DSM-5* (range, 0-80 points; higher scores indicate worse symptoms).[14]

Patients self-reported their history of treatment by reviewing a list of psychotropic medications with doses representing an adequate trial (treatment-refractory depression was defined as a history of 2 or more medication treatments for at least 6 weeks with standard doses or treatment with electroconvulsive therapy or transcranial magnetic stimulation). Race and ethnicity were collected by self-report using fixed categories of Asian/Pacific Islander, Black/African American, Hispanic, Native American/Alaskan, White, Other/Mixed, and refused. Race was prespecified as a factor, given ancestral group differences in genetic architecture.[15] All clinical visits and prescriptions data were extracted from the electronic medical record.

## Outcomes

Outcomes were assessed at 4, 8, 12, 18, and 24 weeks after randomization by raters blinded to all clinical care and study randomization. Outcome assessments were conducted centrally to reduce variability in data collection and potential unblinding. For the co-primary outcome of treatment initiation, antidepressant medications prescribed within the first 30 days after randomization were characterized based on drug-gene interaction categories specified by the commercial test: no known drug-gene interactions, moderate drug-gene interactions, and substantial drug-gene interactions. If there were overlapping prescriptions, the treatment was characterized based on the medication with the greatest rating of drug-gene interaction. The co-primary outcome of remission from depression symptoms was defined as a binary indicator of a PHQ-9 score of 5 or less at each outcome assessment.

There were 2 secondary treatment outcomes: (1) response to treatment, which was defined as a binary indicator at each time point of at least a 50% decrease from the baseline PHQ-9 score, and (2) the change in PHQ-9 score at each time point.

Post hoc analyses examined intervention effects on prescribing in the first 30 days and assessment completion and the influence of missing data on the co-primary outcomes.

## Sample Size Calculation

The sample size was based on the comparison between the randomization groups on the primary remission hypothesis.[16] Loss due to dropout was estimated at 20% and was expected to be similar between the 2 groups. The mean correlation between time points (accounting for within-clinician and within-patient dependence) was estimated to be 0.4. Using these parameters, the planned sample of 1000 per group yielded 80% power for a group difference in remission rates of 35% (pharmacogenomic-guided group) and 30% (usual care group), and power of 89% for rates of 25% vs 20%. These rates were based on response rates in prior depression trials and intervention effects that the investigators considered clinically meaningful.[2,3] For the treatment initiation hypothesis, comparing the groups on a 3-level ordinal measure, a proportional odds regression model yielded 80% power to detect an odds ratio of 1.29 or higher between the randomization groups.

## Statistical Analysis

The analyses were performed using SAS version 9.4 (SAS Institute) and STATA/MP version 17.0 (StataCorp) software. Two-sided tests were used for all outcomes, with an $\alpha$ level of 2.5% for the co-primary hypotheses and 5% for secondary outcomes. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Primary and secondary outcomes were compared using generalized estimating equations (GEEs) logistic regression models, with site included as a categorical explanatory variable and patient responses as repeated measures within clinicians, with the group variable as the only other explanatory variable. Estimates of risks, and risk differences across pharmacogenomic-guided groups, were obtained from these models, with confidence intervals based on $\delta$-method standard errors. Cumulative odds models were used for the ordinal 30-day drug-gene interaction response; the proportional odds hypothesis was rejected ($\chi^2[1] = 25.0$; $P < .001$) so the effect of intervention was allowed to vary across the cumulative logits. For the repeated-measures analyses, the models included factors for time and group × time interactions. Compound symmetry was used as the working correlation structure for the binary responses and independence for the ordinal response.

Table 1. Participating Clinician Characteristics in Relationship to the Number of Their Patients Randomized in the Trial

| Characteristic | No. (%) | | |
|---|---|---|---|
| | Clinicians with 1-5 randomizations | Clinicians with 6-10 randomizations | Clinicians with ≥11 randomizations |
| No. | 276 | 62 | 48 |
| Age, y[a] | | | |
| <41 | 92 (33) | 25 (40) | 16 (33) |
| 41-60 | 138 (50) | 26 (42) | 21 (44) |
| >60 | 42 (15) | 10 (16) | 11 (23) |
| Sex | | | |
| Female | 162 (59) | 42 (68) | 39 (81) |
| Male | 114 (41) | 20 (32) | 9 (19) |
| Race (self-report) | | | |
| African American/Black | 15 (4) | 2 (1) | 3 (1) |
| American Indian/Alaskan | 1 (0) | 0 | 0 |
| Asian | 54 (14) | 8 (2) | 8 (2) |
| Pacific Islander or Native Hawaiian | 1 (0) | 0 | 0 |
| White | 176 (46) | 45 (12) | 34 (9) |
| Other[b] | 4 (1) | 2 (1) | 0 |
| Preferred not to answer | 18 (5) | 4 (1) | 2 (1) |
| Selected >1 category | 7 (2) | 1 (<1) | 1 (<1) |
| 50% or more of current work time spent in clinical care | 249 (90) | 61 (98) | 46 (96) |
| Professional degree | | | |
| Physician | 216 (78) | 45 (73) | 22 (46) |
| Advanced practice nurse/ physician assistant | 52 (19) | 12 (19) | 24 (50) |
| PharmD | 8 (3) | 5 (8) | 2 (4) |
| Practice location | | | |
| Integrated care[c] | 24 (9) | 9 (15) | 12 (25) |
| Primary care | 74 (27) | 5 (8) | 3 (6) |
| Specialty mental health | 178 (64) | 48 (77) | 33 (69) |

[a] Age asked as a categorical response (<30, 31-40, 41-50, 51-60, >60 years).

[b] Other includes those who responded as "other" but could not be categorized.

[c] Mental health clinicians working within a primary care setting in a collaborative care practice.

In subgroup analyses, prespecified additional covariates (age [<60, ≥60 years], race and ethnicity [Black/African American, White, other], sex [female, male], presence of PTSD, clinician-level location of care [primary care, mental health care, or integrated care], and 1 post hoc covariate (treatment-refractory depression) were included in the models described above to examine the sensitivity of the estimated intervention effect to random imbalances in the distributions of these variables. To examine possible heterogeneity of effect, additional analyses included interactions between these variables and the intervention variable. Here, each variable and its interaction with the pharmacogenomic-guided group were included separately in extensions of the GEE model for the primary analyses, and estimates of the intervention effects within each level of the variable, and the interaction effect, were reported. To account for data not being missing completely at random, the models for the repeated remission rates were extended to consider inverse-probability-weighted selection models (valid under missing at random assumption) and pattern mixture models[17] (valid under a particular missing not at random assumption). The statistical analysis plan is in Supplement 2.

## Results

### Clinicians

A total of 676 clinicians consented to participate in the study. While the protocol capped the number of randomized patients per clinician at 30, the distribution of the number of randomizations per clinician varied. Among clinicians who had at least 1 randomized patient, those with 50% or greater time in clinical practice, who practiced in a mental health clinic, or were advanced practice nurses had more randomized patients (**Table 1**); additional referral information is in eTable 2 in Supplement 3.

### Patients

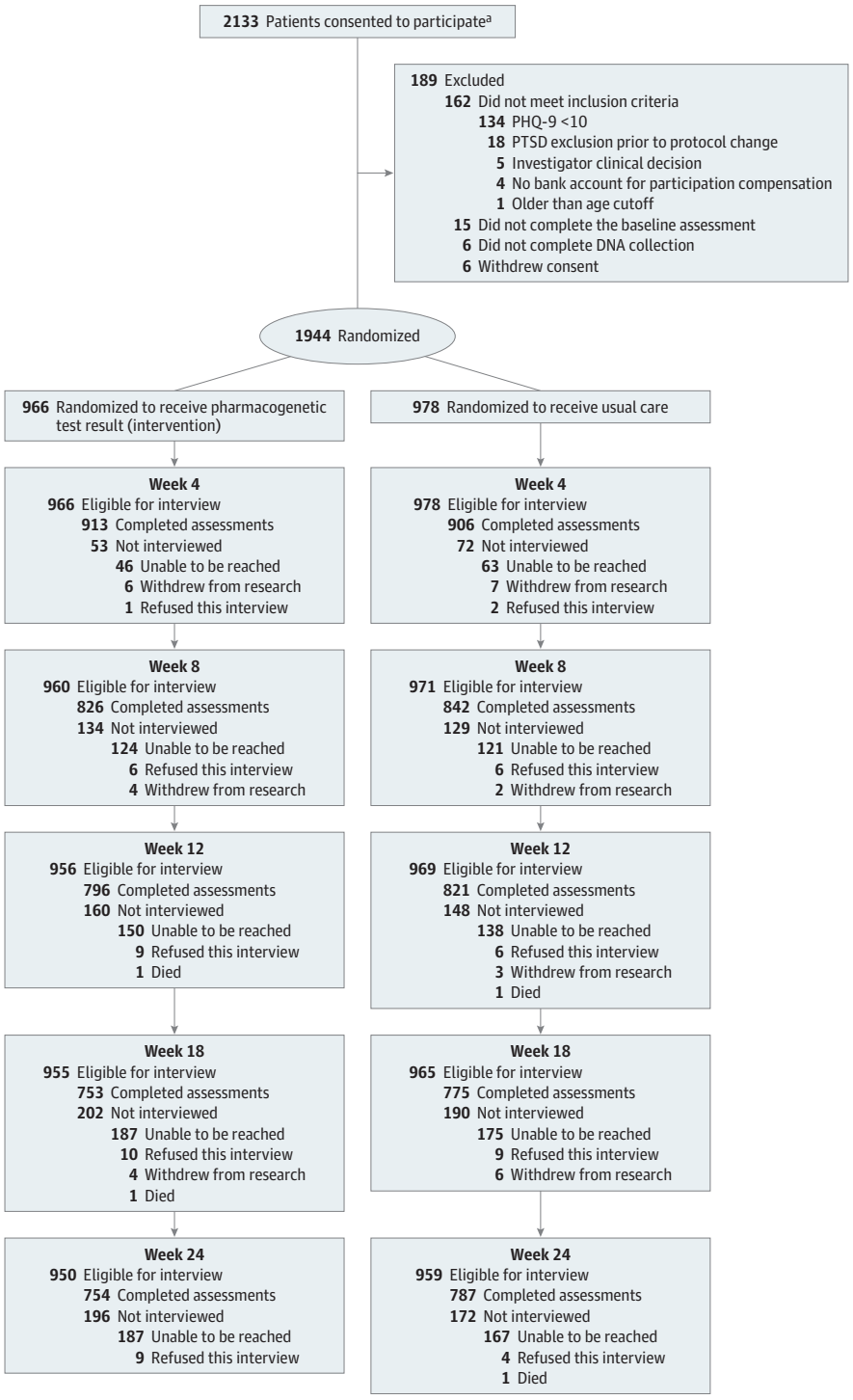
Between 2017 and 2021, a total of 2133 patients consented to participate (**Figure**), of whom 1944 were randomized. Demographic and clinical characteristics were similar for the 2 study groups (**Table 2**).

### Co–Primary Outcomes

#### Treatment Initiation

As shown in **Table 3**, among patients who received an antidepressant prescription, the (nonproportional odds) cumulative

Figure. Screening, Enrollment, Randomization, and Outcomes Among Individuals in the Study of Antidepressant Pharmacogenomics




PHQ-9 indicates Patient Health Questionnaire–9; PTSD, posttraumatic stress disorder.

[a] The number of patients approached by clinicians was not collected.

logit model showed that the pharmacogenomic-guided group was more likely to receive an antidepressant with no potential drug-gene interaction, while the usual care group was more likely to receive a drug with mild potential drug-gene interaction ($\chi^2 = 169.2$; $P < .001$) (no drug-gene interaction vs moderate/substantial interaction: odds ratio [OR], 4.32 [95% CI, 3.47 to 5.39]; $P < .001$) and no/moderate vs substantial interaction: OR, 2.08 [95% CI, 1.52 to 2.84]; $P = .005$). The estimated risks of none, moderate, and substantial interaction for the pharmacogenomic-guided group were 59.3%, 30.0%, and 10.7% compared with 25.7%, 54.6%, and 19.7% for the usual care group, respectively (estimated risk difference, 33.6% [95% CI, 28.9%

Table 2. Patient Baseline Demographics, Social, and Clinical Characteristics

| Characteristic | Group, No. (%) | |
|---|---|---|
| | Pharmacogenomic guided | Usual care |
| No. | 966 | 978 |
| Patient characteristics | | |
| Age, mean (SD), y | 48 (15) | 47 (15) |
| Sex | | |
| Female | 229 (24) | 262 (27) |
| Male | 737 (76) | 716 (73) |
| Race | | |
| African American/Black | 185 (19) | 167 (17) |
| Asian Pacific Islander | 31 (3) | 24 (3) |
| Native American/Alaskan | 10 (1) | 9 (1) |
| White | 644 (67) | 688 (70) |
| Other/mixed[a] | 90 (9) | 84 (9) |
| Refused | 6 (1) | 6 (1) |
| Hispanic ethnicity | 113 (12) | 104 (11) |
| Financial status | | |
| Have just enough to get along | 482 (50) | 492 (50) |
| Are comfortable | 338 (35) | 352 (36) |
| Can't make ends meet | 127 (13) | 116 (12) |
| Clinical symptoms | | |
| PHQ-9 score, inclusion criteria >9, mean (SD)[b] | 17.5 (4.3) | 17.5 (4.3) |
| Treatment refractory[c] | 288 (30) | 301 (31) |
| GAD-7 score, mean (SD)[d] | 14.1 (4.8) | 13.9 (5.0) |
| PTSD presence[e] | 566 (59) | 562 (58) |
| PCL-5 score in those with PTSD, mean (SD)[f] | 51.5 (12.0) | 51.8 (12.0) |
| Suicidal ideation (C-SSRS) (moderate or higher risk), No./total (%)[g] | 187/597 (31) | 190/596 (32) |
| Alcohol use | | |
| Those with at-risk drinking[h] | 219 (23) | 230 (24) |
| Drinks per week, median (IQR) | 0 (0-3) | 0 (0-4) |
| Recent regular (last 3 mo) marijuana use[i] | 227 (23) | 238 (24) |
| Other recent regular (last 3 mo) drug use[i] | 15 (2) | 13 (1) |
| Current tobacco use[i] | 256 (27) | 250 (26) |
| VR-12 composite score, mean (SD)[j] | | |
| Mental | 23.8 (10.6) | 24.9 (10.2) |
| Physical | 37.9 (13.4) | 36.4 (13.1) |

Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; GAD-7, Generalized Anxiety Disorder-7; PCL-5, PTSD Checklist for *DSM-5*; PHQ-9, Patient Health Questionnaire-9; PTSD, posttraumatic stress disorder; VR-12, Veterans RAND 12-item Health Survey.

[a] "Other/mixed" was not specified and was the term used during data collection.

[b] Range, 0-27 points; higher scores indicate worse symptoms.

[c] Treatment-refractory depression defined as self-reported history of 2 or more medication treatments for at least 6 weeks with standard doses or treatment with electroconvulsive therapy or transcranial magnetic stimulation.

[d] Range, 0-21 points; higher scores indicate worse symptoms.

[e] PTSD diagnosis derived using *DSM* criteria applied to the PCL-5 assessment.

[f] Range, 0-80 points; higher scores indicate worse symptoms.

[g] Seven yes/no questions, scored as no, low, moderate, or high risk for suicide.

[h] At risk drinking defined as >14 drinks per week for men, >10 drinks per week for women, or >3 binges in the last 3 months for either sex.

[i] A modified version of the National Institute on Drug Abuse's Alcohol, Smoking, and Substance Involvement Screening Test to measure substance use as present or absent in the last 30 days. Other drug use includes cocaine, amphetamines, opioids, inhalants, sedatives, and hallucinogens.

[j] Two subscores (mental health [Mental Component Summary] and physical health [Physical Component Summary]; range, 0-100; higher scores indicate higher function) and tobacco use (yes/no).

to 38.4%], $P < .001$ for none; −24.6% [95% CI, −29.5% to −19.7%], $P < .001$ for moderate; and −9.0% [95% CI, −12.7% to −5.3%], $P < .001$ for substantial interaction).

### Remission

**Table 4** shows the remission rates by group for each study week, with estimated ORs from a group × time interaction model. There was a significant main effect of group, with greater rates of remission in the pharmacogenomic-guided group over the 24 weeks (OR, 1.28 [95% CI, 1.05 to 1.57]; $P = .02$; absolute risk difference, 2.8% [95% CI, 0.6% to 5.1%]) (Table 4). The group × time interaction was not significant ($P = .08$). There were significant differences between the groups at 8 and 12 weeks and no significant differences

Table 3. Prescription Antidepressant Use in the First 30 Days After Randomization

| | Group | | Estimated (95% CI) | | |
|---|---|---|---|---|---|
| | Pharmacogenomic guided | Usual care | Risk difference, % | Odds ratio | *P* value |
| No. | 966 | 978 | | | |
| Antidepressant prescribed in the first 30 d, No. (%) | 727 (75) | 679 (69) | −5.8 (−9.9 to −1.7) | 0.74 (0.60 to 0.92) | .005 |
| Level of prescribed antidepressant/gene interaction, No./total (%) | | | | | |
| None | 433/727 (60) | 173/679 (25) | 33.6 (28.9 to 38.4) | | |
| Moderate | 215/727 (30) | 373/679 (55) | −24.6 (−29.5 to −19.7) | | |
| Substantial | 79/727 (11) | 133/679 (20) | −9.0 (−12.7 to −5.3) | | |
| None vs moderate and substantial | 433/727 (60) vs 294/727 (40) | 173/679 (26) vs 506/679 (74) | | 0.19 (0.23-0.29) | <.001 |
| None and moderate vs substantial | 648/727 (89) vs 79/727 (11) | 546/679 (80) vs 133/679 (20) | | 2.08 (1.52-2.84) | .005 |

Table 4. Effect of Immediate Return of Pharmacogenetic Results (Pharmacogenomic-Guided Group) vs Usual Care on Depression Remission, Response, and Symptom Improvement

| | Group, No. (%) | | Estimated within time point effect of intervention | | | Pooled effect of group over time | | |
|---|---|---|---|---|---|---|---|---|
| | Pharmacogenomic guided | Usual care | RD, % (95% CI) | OR (95% CI) | *P* value | OR (95% CI) | RD (95% CI), % | *P* value |
| **Remission (PHQ-9 ≤ 5)** | | | | | | | | |
| 4 wk | 86 (9.4) | 72 (8.0) | 1.5 (−1.2 to 4.1) | 1.21 (0.82 to 1.59) | .27 | | | |
| 8 wk | 121 (14.7) | 95 (11.3) | 3.6 (0.5 to 6.6) | 1.38 (1.05 to 1.81) | .02 | | | |
| 12 wk | 131 (16.5) | 92 (11.2) | 5.4 (2.2 to 8.6) | 1.59 (1.21 to 2.10) | .001 | 1.28 (1.05 to 1.57) | 2.8 (0.6 to 5.1) | .02 |
| 18 wk | 119 (15.8) | 105 (13.6) | 2.4 (−0.8 to 5.5) | 1.21 (0.94 to 1.57) | .14 | | | |
| 24 wk | 130 (17.2) | 126 (16.0) | 1.5 (−2.4 to 5.3) | 1.11 (0.84 to 1.47) | .45 | | | |
| **Response (>50% decrease in PHQ-9 total score)** | | | | | | | | |
| 4 wk | 158 (17.3) | 149 (16.5) | 0.9 (−2.3 to 4.0) | 1.07 (0.85 to 1.34) | .58 | | | |
| 8 wk | 216 (26.2) | 176 (20.9) | 5.5 (1.7 to 9.3) | 1.36 (1.10 to 1.70) | .005 | | | |
| 12 wk | 239 (30.0) | 195 (23.8) | 6.6 (2.1 to 11.0) | 1.41 (1.12 to 1.77) | .004 | 1.25 (1.07 to 1.46) | 4.0 (1.2 to 6.8) | .005 |
| 18 wk | 214 (28.4) | 204 (26.3) | 2.4 (−1.6 to 6.4) | 1.13 (0.92 to 1.39) | .23 | | | |
| 24 wk | 242 (32.1) | 216 (27.5) | 5.1 (0.6 to 9.6) | 1.29 (1.03 to 1.60) | .03 | | | |
| | **Mean (SD)** | | **Mean difference (95% CI)** | | | **Difference (95% CI)** | | |
| **Symptom improvement (decrease in PHQ-9 total score)** | | | | | | | | |
| 4 wk | 3.4 (5.0) | 3.1 (4.9) | 0.25 (−0.20 to 0.70) | | .27 | | | |
| 8 wk | 4.6 (5.6) | 4.1 (5.1) | 0.51 (0.03 to 1.00) | | .04 | | | |
| 12 wk | 5.3 (5.7) | 4.4 (5.2) | 0.96 (0.42 to 1.50) | | <.001 | 0.56 (0.17 to 0.95) | | .005 |
| 18 wk | 5.1 (5.8) | 4.7 (5.5) | 0.47 (−0.05 to 1.00) | | .08 | | | |
| 24 wk | 5.4 (5.9) | 4.8 (5.6) | 0.65 (0.10 to 1.19) | | .02 | | | |

Abbreviations: OR, odds ratio; PHQ-9, Patient Health Questionnaire-9; RD, risk difference.

between groups at 4, 18, and 24 weeks. At 24 weeks, 130 patients in the pharmacogenomic-guided group and 126 in the usual care group met remission criteria (risk difference, 1.5% [95% CI, −2.4% to 5.3%]; *P* = .45).

## Secondary Outcomes

Secondary outcomes of response to treatment and reduction in symptom severity also favored the pharmacogenomic-guided group (OR, 1.25 [95% CI, 1.07 to 1.46]; *P* = .005; absolute risk difference, 4.0% [95% CI, 1.2% to 6.8%] and mean difference in reduction between groups, 0.56 [95% CI, 0.17 to 0.95]; *P* = .005], respectively) (Table 4), with nonsignificant group × time effects (*P* = .09 and *P* = .12, respectively). There was no significant difference in response rates (32.1% [95% CI, 28.9% to 35.8%] vs 27.5% [95% CI, 24.1% to 30.4%]; risk difference, 5.1% [95% CI, 0.6% to 9.6%]; *P* = .02) at 24 weeks; however, symptom improvement was larger at 24 weeks in the pharmacogenomic-guided group (mean, 5.4 [95% CI, 5.0 to 5.8] vs 4.8 [95% CI, 4.4 to 5.2]; mean symptom difference, 0.65 [95% CI, 0.10 to 1.19]; *P* = .02).

## Subgroup Analyses

There were no significant intervention × covariate interactions for either medication treatment choice (none, moderate, substantial) (eTable 3a in Supplement 3) or remission (eTable 4a in Supplement 3). Adjustments for covariates yielded similar results for treatment initiation and remission (eTables 3a and 4a in Supplement 3). Among the additional covariates, PTSD, race, and treatment refractory depression were significantly associated with treatment choice (eTables 3a and 3b in Supplement 3) and remission was significantly affected by race, practice location, and the presence of PTSD or treatment-refractory depression (eTables 4a and 4b in Supplement 3).

### Post Hoc Outcomes

A higher proportion of patients in the pharmacogenomic-guided group received an antidepressant prescription in the first 30 days than in the usual care group (OR, 1.35 [95% CI, 1.09 to 1.67]; $P = .005$; risk difference, 5.8% [95% CI, 1.7% to 9.9%]). There were no significant intervention × covariate interactions for receiving an antidepressant (eTable 5a in Supplement 3). Adjustments for covariates yielded similar results for receiving an antidepressant (eTable 5a in Supplement 3). None of the covariates were significantly associated with receiving an antidepressant (eTables 5a and 5b in Supplement 3). Time to first prescription is shown in the eFigure in Supplement 3.

For treatment outcomes, rates of assessment completion (Figure) were similar for the 2 groups (787/978 = 80.5% in the usual care group, 754/966 = 78.1% in the pharmacogenomic-guided group [OR, 0.86 {95% CI, 0.69 to 1.07}; $P = .18$; risk difference, −2.4% {95% CI, −5.9% to 1.1%}]). An inverse-probability-weighted GEE model showed a significant effect of group on remission outcome (OR, 1.32 [95% CI, 1.06 to 1.66]; $P = .02$; risk difference, 3.1% [95% CI, 0.6% to 5.7%]), and a pattern mixture analysis (based on classifying dropout times as ≤12 weeks, 18 weeks, or completion) showed a similar effect (OR, 1.29 [95% CI, 1.05 to 1.57]; $P = .02$; risk difference, 2.9% [95% CI, 0.6% to 5.1%]). Thus, we saw agreement between the original analyses and these analyses under different missing data assumptions, suggesting our main results were not sensitive to missing data.

### Adverse Events

There were no identified harms to patients related to the intervention.

## Discussion

Among patients with MDD, the provision of pharmacogenomic testing for drug-gene interactions reduced prescription of medications with predicted drug-gene interactions compared with usual care. Overall, there were small positive effects on symptom remission over the 24 weeks with peak differences early in the trial and no significant difference in remission at 24 weeks. The secondary outcomes of response and symptom reduction followed similar patterns.

This study was designed to test differences in outcomes for all randomized patients. However, many of the patients had no or only moderate predicted drug-gene interactions. In those patients, pharmacogenomic testing would have provided no relevant clinical information in the decisional process of choosing a medication and no effect on depression outcomes. The smaller subgroup with predicted substantial drug-gene interactions would be a more appropriate target of testing, but until tested, these individuals cannot be identified. In post hoc analysis of the GUIDED Trial, Thase et al[18] found a larger difference in outcomes among patients treated with a medication with drug-gene interactions compared with all others but this is a nonrandomized effect and vulnerable to substantial interpretation bias. Enriching the randomized sample for patients with potential drug-gene interactions should be considered in future study designs. Ultimately, the clinical decision of whether to use pharmacogenomic testing should be guided by a risk-benefit consideration. The negative consequences of pharmacogenomic testing are low and relate principally to cost. While the benefit on a population level may be limited, there may be value in the aggregate and to the individual patient.

Clinician behavior was also a focus of the trial. At the onset, most clinicians had limited experience with pharmacogenomic testing,[19,20] and no effort was made to account for differences in knowledge among them. There was a substantial effort during the trial to educate clinicians and patients using educational videos, talks, written materials, and one-on-one consultation with local site investigators.

Overall, the remission rates and effect sizes were similar to those reported in the GUIDED Trial.[4] However, the present study differed in several ways, including having a larger sample, being longer in duration, using frontline clinical staff including those in primary care, and using a repeated-measures analytic approach. As a pragmatic trial, inclusion and exclusion criteria were ascertained by the referring clinician. While the sample comprised only patients receiving care at VA medical centers with a higher proportion of males than a community sample, racial minority representation was higher than in typical clinical trials. Remission rates were significantly affected by subgroups.

### Limitations

This study has several limitations. First, there was no attempt to blind either the clinician or patient in the study. Thus, the modest effects in the pharmacogenomic-guided group could be a placebo-type effect.

Second, the trial was not powered to evaluate outcomes such as the effect of changes in dosing in the pharmacogenomic-guided group among patients with predicted drug-gene interactions, the presence of adverse drug reactions, the effect of medication adherence by patients, or the effect of antidepressant switches after randomization.

Third, because the trial used a proprietary pharmacogenomic test, results may not translate to other commercial products. The proprietary algorithm used to make recommendations about drug-gene interactions may not align with recommendations from groups such as the Clinical Pharmacogenetics Implementation Consortium, a nonprofit organization that provides recommendations for drug-gene interaction.[21]

Fourth, many patients had a delay of unclear meaning and importance in initiating a new episode of treatment though post hoc analysis showed the delay decreased rapidly over the trial. None of the covariates were associated with this delay.

## Conclusions

Among patients with MDD, provision of pharmacogenomic testing for drug-gene interactions reduced prescription of medications with predicted drug-gene interactions compared with usual care. Provision of test results had small nonpersistent effects on symptom remission.

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