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Precision medicine for depression: development of a decision-support tool based on the PRIME randomized controlled trial

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ABSTRACT (149 words)

Many patients with major depressive disorder (MDD) do not respond to their first antidepressant, and clinicians lack an empirical basis for deciding whether to continue or change treatment after an initial trial. We analysed the Precision Medicine in Mental Health Care (PRIME) pragmatic randomized controlled trial, in which 1,944 US veterans were randomized to usual care enhanced by pharmacogenetic testing or to usual care alone. Using decision tree analysis in the 1,307 participants who had not responded after four weeks, four characteristics separated those with the highest (39.9±10.5%) and the lowest (11.1±3.0%) likelihood of week-12 treatment response: symptom improvement at week 4, better physical health, availability of pharmacogenetic test results, and absence of post-traumatic stress disorder. The resulting decision-support tool identified 77% of week-4 partial and non-responders as candidates for a treatment change. This preliminary tool requires validation in independent samples before prospective clinical evaluation.

Trial registration: NCT03170362 (clinicaltrials.gov)

Introduction

Many patients do not respond rapidly (within 4 weeks) to their antidepressant and are faced with the decision of whether to stay the course, hoping for an eventual response, or to change treatments [1,2]. This is a common and highly fraught decision, as staying the course with an ultimately ineffective antidepressant exposes the patient to persistent depression with its associated suffering and risks such as suicide [3,4]. However, prematurely discontinuing an antidepressant and changing treatment expose the patient to new risks and unknowns [2]. While some studies have reported that a lack of treatment response after 2-4 weeks of starting an antidepressant is sufficient to change treatment [5,6], other studies have shown that a substantial proportion of patients do eventually respond with longer treatment [2,7]. Early identification of patients who are unlikely to benefit from prolonged treatment would enable a more efficient transition to an alternative treatment and improve patient outcomes.

A growing number of clinical markers are proposed to predict and improve treatment outcomes [8,9]. However, despite this growing body of evidence, these markers are not used meaningfully in real-world clinical settings [10]. A decision-support tool that organizes easily obtainable demographic, clinical, and biological characteristics into a hierarchical structure may help to translate complex and heterogeneous evidence into actionable clinical decisions that can be used to personalize treatment advancement.

Decision tree analysis can evaluate multiple intercorrelated patient characteristics simultaneously, allowing the integration of both baseline and early treatment variables, to select a small number of predictors that can meaningfully separate subgroups of patients with different outcomes [11,12].

Using decision tree analysis, our previous work identified subgroups of patients that have two or more fold difference in their likelihood of attaining treatment response with different pharmacological and non-pharmacological interventions [7,12,13]. We previously showed in three different datasets from randomized controlled trials (RCTs) that four weeks is sufficient to determine which older patients should change treatment [7,12,14]. It is important to determine whether this is also the case in younger patients.

The Precision Medicine in Mental Health Care (PRIME) study was a multisite pragmatic RCT that examined whether pharmacogenetic testing could improve treatment outcomes in mixed-age US veterans with MDD [15]. Previous studies have reported mixed findings on whether pharmacogenetic testing can improve clinical outcomes [15-17]. This suggests that there may be heterogeneity in the extent to which a patient can benefit from pharmacogenetic testing, similar to most psychiatric interventions [1,18,19].

In this context, we aimed to use the PRIME dataset to construct an empirically derived decision-support tool that would enable the early identification of patients who can stay on their current antidepressant and those who should change their treatment. Based on our previous work in older patients with MDD [7,14] and the published findings from the PRIME study [15], we hypothesized that the decision-support tool would include being defined as having treatment-resistance and not having early symptom improvement after four weeks of antidepressant treatment.

Results

Participant characteristics

Participant characteristics of the 1 307 participants included in decision tree analyses are summarized in Table 1. Of 269 participants who attained treatment response at week-4, 176 attained treatment response at week-12 (65.4%). Of 1 307 participants who did not attain treatment response at week-4, 246 attained treatment response at week-12 (18.8%). Of the 29 potential predictors, 14 survived variable pre-selection and were considered in the decision tree analysis (Supplementary Results).

Decision tree analysis predicting treatment response at week-12

In the five training trees, the average rightmost test PPV was 39.9 ± 10.5% and the average leftmost test PPV was 11.1 ± 3.0%. Based on these five training trees, the following five variables were significant predictors of not attaining treatment response at week-12: not attaining partial response (from 25% to less than 50% improvement from baseline in depressive symptoms) at week-4; poorer physical health at baseline (VR-12 PCS score less than 32.9; score higher than 50 indicates above-average health; score lower than 50 indicates below-average health); receiving usual care without pharmacogenetic testing results; having comorbid PTSD at baseline; and having more adverse effects at week-4 (total adverse effect score ≥ 2).

Supplementary Figure 1 presents the final decision tree trained on the entire dataset (i.e., all five subsets) and pruned to only include the significant predictors. This resulted in four predictors being retained in the final decision tree. While having more adverse effects at week-4 was a predictor in 3 training trees, it was not retained by this final decision tree trained on the entire sample, indicating that its association with week-12 response was not stable. In this final

decision tree, the likelihood of attaining week-12 treatment response in participants with the highest likelihood of doing so (i.e., rightmost PPV) was 40.5%. The likelihood of attaining week-12 treatment response in participants with the lowest likelihood of doing so (i.e., leftmost PPV) was 9.5%. Using this decision tree, 1000 of 1307 (77%) partial and non-responders at week-4 were identified as having less than 20% likelihood of attaining treatment response with 8 additional weeks of treatment.

Discrimination of the final decision tree, calculated across its seven terminal nodes, was modest (AUC = .69; Brier score = .14; Supplementary Methods). This is expected, as the tree was constructed to separate the subgroups that are most vs. least likely to respond rather than to rank all participants optimally. A binary logistic regression using the four predictors retained by the decision tree was fitted in the same participants. The model was statistically significant, $\chi^2(4) = 102.91$, $p < .001$, explaining 12.3% of the variance in week-12 treatment response (Nagelkerke R^2), and it discriminated no better than the decision tree (AUC = .70). All four predictors were independently associated with week-12 treatment response (Supplementary Table 1).

In exploratory analyses examining week-24 treatment response, the pharmacogenetic-enhanced usual care was not selected as a predictor (Supplementary Results).

The decision-support tool for identifying patients who should continue vs. change their current treatment after four weeks of being on an antidepressant is shown in Figure 2.

Discussion

We analyzed data from PRIME, a large pragmatic RCT involving 1 944 participants with MDD to create an empirically derived decision-support tool for the early identification of patients who can stay on their current treatment vs. change their treatment rather than staying longer on an antidepressant that will eventually prove to be ineffective. Our results suggest that patients with MDD may be candidates for an early change in treatment if they do not respond to four weeks of treatment with an antidepressant based on the use of measurement-based care and: their depression severity has decreased by less than 25% from baseline; they have poorer physical health; or have comorbid PTSD. Conversely, they should remain on their current antidepressant after four weeks of treatment if: their depression severity has decreased by 25% or more from baseline; they have a better physical health; and they do not have comorbid PTSD. Our findings illustrate the usefulness of decision tree analysis to create decision-support tools for answering clinically meaningful questions.

In our decision tree analysis, early symptom improvement at week-4 was the strongest predictor of eventual treatment response, consistent with previous studies of pharmacotherapy in MDD[6,7,12] and supporting the guideline recommendation to re-evaluate antidepressant effect with a standardized scale at week-4[20]. Decision tree analysis also ranked previously identified predictors against one another rather than testing each in isolation, placing early improvement above other predictors in the hierarchy. In addition, it quantified how widely these predictors can separate future responders from non-responders, so that a decision can be made as to whether it is clinically meaningful. In this sample, a four-fold separation was shown between those who are most vs. least likely to respond, comparable to the separation obtained in other samples, such as older patients with MDD[7] and patients with MDD and comorbid at-risk drinking[13]. Decision tree

analysis achieved discrimination comparable to logistic regression while also adding explicit thresholds and a hierarchy showing how predictors combine in an individual patient, making the result usable at the point of care.

Participants whose clinicians had pharmacogenetic test results available were more likely to respond at week-12 but not at week-24, matching the pattern reported in the primary PRIME analysis[15] and in the wider literature, in which pharmacogenetic guidance accelerates response without changing longer-term outcomes[17,21]. In our analysis, pharmacogenetic testing was the weakest of the four predictors retained and entered a single branch containing 104 of the 1,307 participants (8%). The degree of possible negative pharmacogenetic interaction of the antidepressant was not a significant predictor, suggesting that benefit of testing cannot be attributable to the drug selected. Expectancy effects or other changes in prescriber behaviour are plausible alternatives. The availability of test results is therefore better understood as a feature of how care was delivered in this trial than as a stable patient-level predictor, and further study is needed to determine whether pharmacogenetic testing has a role at this stage of treatment.

In the current sample of middle-aged veterans, decision tree analyses identified two other predictors that have not emerged in previous analyses: poorer (i.e., below average) physical health and comorbid PTSD. This is consistent with a meta-analysis of 26 studies in adults with MDD that showed an association between physical comorbidities and poorer antidepressant outcomes [22]. A bidirectional relationship between MDD and physical illness has been described in the literature [23-27]. Identification of PTSD as a predictor of poorer outcome of pharmacotherapy in the current sample of veterans with MDD is consistent with the results of the

VAST-D study that involved 522 veterans with MDD [28]. To prevent poor treatment outcomes, patients with MDD and PTSD may require a different treatment approach.

A decision-support tool that recommends earlier treatment change might be expected to increase unnecessary switching, but this analysis suggests otherwise. The tool recommends a change for 1,000 of the 1,307 week-4 partial and non-responders (77%), whereas 1,061 (81%) of them did not respond after eight further weeks. This proportion is consistent with the approximately half of patients who do not respond to a full first-step antidepressant course delivered with measurement-based care[29], given that the present sample already excludes those who had responded by week-4. The concern of a premature switch in treatment remains clinically relevant. In patients for whom a premature switch carries greater risk, such as in older adults, the decision tree optimizing specificity can be used (Supplementary Figure 2).

Our analysis has some limitations. First, it is based on clinical trial data with systematic collection of symptom severity; we do not know whether the same predictors would be identified in a clinical setting. We also did not test the model on an independent sample. Instead, we used five-fold cross-validation, which is an internal validation approach in predictive modeling[30]. The analytic methods used here have previously been applied in decision tree analyses of datasets from other RCTs involving older adults with MDD [7,12], supporting the robustness and reproducibility of this approach. However, while this approach reduces the risk of overfitting and provides an estimate of model performance in held-out data, it is not a substitute for external validation. Validation in an independent sample is needed before this decision-support tool is ready for clinical implementation. Second, some previously identified predictors such as illness

duration, the number of previous major depressive episodes, and chronicity of the current episode were not collected in PRIME. The PRIME cohort consisted largely of middle-aged US veterans, among whom the prevalence of PTSD is higher than the general population[31]. Lastly, our decision tree analysis did not account for patient preference.

In conclusion, our findings suggest that many patients with MDD should advance to the next step in their treatment course after four weeks rather than continuing a treatment that will eventually prove to be futile. The candidates for an early change in treatment are those who have not attained partial response, have below average physical health, or have comorbid PTSD. This decision-support tool has been developed and internally validated. The next step is validation in independent samples, including in non-veteran samples, followed by prospective evaluation in clinical settings.

Methods

Overview

The study design and the primary report of the PRIME clinical trial have been published[15]. The PRIME Care trial protocol was approved by the U.S. Department of Veterans Affairs Central Institutional Review Board. All participants provided written informed consent prior to enrollment. Briefly, US veterans aged 18 – 80 years old with a diagnosis of MDD and a plan to start a new antidepressant were enrolled. Participants (N = 1 944) were openly randomized 1:1 to receiving usual care enhanced by the results of a standard pharmacogenetic panel [32] from their primary care providers or outpatient psychiatrists (i.e., pharmacogenetic-enhanced usual care) vs. usual care. Potential psychotropic drug-gene interactions were categorized as “none known”

(coded as 1 shown as green), “moderate” (2, shown as yellow), or “substantial” (3, shown as red). The accompanying suggested management for each category were: green - “use as directed”; yellow - “use with caution”; and red - “use with increased caution and more frequent monitoring”[15]. Otherwise, participants in both groups received usual care, according to the providers’ routine practice.

The participants completed a baseline assessment and were monitored at weeks 4, 8, 12, 18, and 24 with the 9-item Patient Health Questionnaire (PHQ-9) [33] and a self-rating of antidepressant adverse effects (headache, nausea, vomiting, sexual dysfunction, diarrhea, and constipation) as “none (coded as 0)”, “mild (1)”, “moderate (2)”, or “interfering (3).”

Participant characteristics

The PRIME RCT dataset included 1 944 participants. The decision tree analyses included 1 307 of the 1 944 randomized participants after excluding: 125 who did not complete the PHQ-9 at week-4; 307 who had already responded by week-4 (with treatment response defined as a 50% or more reduction from baseline in the PHQ-9 score) and would not be candidates for changing treatment (of which 269 had week-12 PHQ-9 scores); and 205 of the remaining participants who did not complete the PHQ-9 at week-12 (Figure 1). There was an equal proportion of participants receiving usual care enhanced by pharmacogenetics and participants receiving usual care included in the analysis (Table 1). We focused on treatment response rather than remission because the goal of the decision-support tool is to identify patients who are expected to improve substantially if they continue their current treatment, rather than to identify patients who would be remitted (i.e., free of depression). A clinician would not change treatment on a patient who

had attained treatment response by week-4 and instead would continue the treatment for longer until remission is attained. Furthermore, the criteria for remission differs depending on the scale used. As the definition of treatment response is based on percent symptom reduction, it allows for a broader application of the results of this analysis[34].

The 29 potential predictors comprised all available baseline participant characteristics, week-4 symptom improvement, and week-4 adverse effects reported in the primary study [15]. These 29 demographic and clinical characteristics were considered in the variable pre-selection process to identify the smaller set of variables that should be included in the decision tree to improve the prediction of treatment response at week-12 (Supplementary Methods). All available data were used. Missing values were handled through available-case analysis.

Decision tree analysis

ROC 5.07 (https://web.stanford.edu/~yesavage/ROC.html) [11] was used for decision tree analysis predicting week-12 treatment response. The procedures used for variable pre-selection and decision tree analysis with five-fold cross validation have been detailed in previous reports from our group [7,13,35] and in Supplementary Methods. Decision tree analysis is robust to multicollinearity and suitable for processing non-parametric data [11,36]. The decision tree analysis was used to construct a decision tree predicting week-12 treatment response in participants who have not attained treatment response at week-4. The decision tree was designed to optimize sensitivity, i.e., to minimize false negative. A false negative corresponds to falsely identifying a participant as having a low likelihood of responding to an antidepressant leading to the premature discontinuation of this antidepressant that would have been effective with longer

289 treatment. Optimizing sensitivity was done to reflect clinical practice in outpatient settings. We
290 present the average test PPV of the rightmost terminal node ± SD (likelihood of attaining
291 eventual treatment response in those who are most likely) and the average test PPV of the
292 leftmost terminal node ± SD (likelihood of attaining eventual treatment response in those who
293 are least likely). The final decision tree diagram that is presented has been trained on the entire
294 dataset and pruned to only include significant predictors. Because the cross-validation training
295 trees are trained on subsets of the sample and the final tree is trained on the entire dataset, the
296 cross-validation trees and the final tree are fitted to different samples. Therefore, the numeric
297 thresholds they select for continuous predictors may differ. We also calculated the area under the
298 receiver operating characteristic curve (AUC) and the Brier score of the final tree. We then fitted
299 logistic regression models to the same participants and predictors to compare the performance of
300 the decision tree with that of a more traditional modelling approach (Supplementary Methods).
301
302 The Supplementary Information presents an alternative decision tree designed to optimize
303 specificity, i.e., to minimize false positives (Supplementary Figure 2). The Supplementary
304 Information also presents two sensitivity analyses: 1) predicting week-24 treatment response;
305 and 2) predicting week-12 remission, defined as a PHQ-9 score of 5 or less as per the primary
306 study [15] (Supplementary Information – Sensitivity Analyses).
307
308 A decision-support tool was constructed using the results of the decision tree analyses for use in
309 patients who had four weeks of antidepressant treatment. This tool makes one of the three
310 recommendations based on the likelihood of attaining eventual treatment response at week-12:
311 continue current treatment (>40% likelihood of attaining treatment response at week-12);

continue or change current treatment (20 – 40% likelihood of attaining treatment response at week-12); change current treatment (<20% likelihood of attaining treatment response at week-12).

Data availability

De-identified participant data from the PRIME Care trial are available on request from the principal investigator of the trial (dave.oslin@va.gov). Access requires approval of a proposal for secondary analysis. The data sharing statement of the primary trial report is available at doi:10.1001/jama.2022.9805.

Code availability

Decision tree analyses were performed in ROC 5.07 (https://web.stanford.edu/~yesavage/ROC.html). No custom code was generated; the analytic specifications required to reproduce the trees are provided in the Methods and Supplementary Methods.

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Wood AE: investigation, writing – review & editing, resources, supervision

Competing interests

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holds and receives support from the Cameron Wilson Chair in Depression Studies at the University of Toronto. He also leads contracted research for Compass Pathfinder Limited. Kloiber S received grants from the Labatt Family Innovation Fund in Brain Health (Department of Psychiatry, University of Toronto), the Max Bell Foundation, the Canadian Centre on Substance Use and Addiction, the Ontario Ministry of Health and Long-Term Care (MOHLTC), the Canadian Institutes of Health Research (CIHR). He has also received an honorarium for past consultations from EmpowerPharm. Kloiber S has been supported by the Academic Scholar Award and the Labatt Family Innovation Fund in Brain Health, Department of Psychiatry, University of Toronto. Lenze EJ received support from the Taylor Family Institute for Innovative Psychiatric Research at Washington University School of Medicine, as well as the Washington University Institute of Clinical and Translational Sciences grant (UL1TR002345) from the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH). He receives research funds (unrelated to this work) from Pritkin, the Balvi Foundation, and the XPrize Foundation. Müller DJ is supported by the Canadian Institutes of Health Research (CIHR), the Ontario Brain Foundation, the Alternate Funding Plan of Ontario, and the Centre for Addiction and Mental Health Foundation. Oslin DW reports receiving grants from the Department of Veterans Affairs (VA) Office of Research and Development (OR&D) and Janssen Pharmaceuticals, and nonfinancial support from Myriad Genetics during the conduct of the primary study; Dr Oslin was the co-chair of the VA/Department of Defense Clinical Practice Guideline for Major Depressive Disorder during the primary study. Mulsant BH received additional support from the Labatt Family Chair in Biology of Depression in Late-Life Adults at the University of Toronto. He holds and receives support from the Labatt Family Chair in Biology of Depression in Late-Life Adults at the University of Toronto. He currently receives or

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453 The following PRIME Care Research Group members report the following competing interests.
454 Dr Aslam reported receiving grants from the VA Research & Development during the conduct of
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462 Dr Hurley reported receiving grants from the VA during the conduct of the study and being
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467 outside the submitted work. Dr Ostacher reported receiving personal fees from Janssen (Johnson
468 & Johnson) and Neurocrine and grants from Otsuka and Freespira (formerly Palo Alto Health
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FIGURE LEGENDS

Figure 1 Title: Participant inclusion and timeline for collection of participant characteristics and outcomes

Figure 1 Footnote: *Abbreviations:* Generalized Anxiety Disorder – 7 items (GAD-7), Patient Health Questionnaire – 9 items (PHQ-9), Post Traumatic Stress Disorder (PTSD)

Figure 2 Title: Decision-support tool for personalizing antidepressant treatment in major depressive disorder.

Figure 2 Footnote: The tool generates one of three recommendations based on the predicted likelihood of attaining treatment response after eight additional weeks of treatment: continue the current treatment (>40% probability of response); consider continuing or changing treatment (20–40% probability); or change treatment (<20% probability). Treatment response indicates ≥50% symptom improvement from baseline. Partial response indicates 25% - <50% symptom improvement from baseline. *Abbreviations*: post-traumatic stress disorder (PTSD), veterans RAND 12-item health survey physical health component summary score (VR12 PCS)

611 **TABLES**

612 Table 1. Participant characteristics at baseline and week-4 that were considered as potential

613 predictors of eventual response at week-12 in 1307 PRIME participants who did not attain

614 treatment response at week-4 (p<0.2 are bolded)

Baseline potential predictors	**Week 12 non-responders (n = 1061)[1]**	**Week 12 responders (n = 246)[1]**	**Whole sample (N = 1307)[1]**	**Statistics[2]**
Pharmacogenetic results available	No: 557 (52.5%) Yes: 504 (47.5%)	No: 106 (43.1%) Yes: 140 (56.9%)	No: 663 (50.7%) Yes: 644 (49.3%)	X^2 = 7.1, df = 1**, p = 0.008**
Sex	Male: 805 (75.9%) Female: 256 (24.1%)	Male: 166 (67.5%) Female: 80 (32.5%)	Male: 971 (74.3%) Female: 336 (25.7%)	X^2 = 7.4, df = 1, **p = 0.007**
Age (years)	48.0 ± 14.7	48.7 ± 14.8	48.2 ± 14.7	F(1, 1305) = 0.5, p = 0.492
Race	Caucasian: 707 (66.6%) Other: 354 (33.4%)	Caucasian: 174 (70.7%) Other: 72 (29.3%)	Caucasian: 881 (67.4%) Other: 426 (32.6%)	X^2 = 1.5, df = 1, p = 0.217
Financial status[1] Can't make ends meet: Just enough to get along: Comfortable:	 136 (13.1%) 535 (51.4%) 369 (35.5%)	 27 (11.1%) 123 (50.4%) 94 (38.5%)	 163 (12.7%) 658 (51.3%) 463 (36.0%)	X^2 = 1.2, df = 2, p = 0.555
Baseline PHQ-9 score	17.8 ± 4.3	17.2 ± 4.1	17.7 ± 4.3	F (1, 1305) = 4.2, p = **0.042**

Treatment resistant depression at baseline	No: 713 (67.2%) Yes: 348 (32.8%)	No: 171 (69.5%) Yes: 75 (30.5%)	No: 884 (67.6%) Yes: 423 (32.4%)	$X^2 = 0.5$, df = 1, p = 0.485
Baseline suicide risk[1]	Low: 445 (66.8%) High: 221 (33.2%)	Low: 105 (70.5%) High: 44 (29.5%)	Low: 550 (67.5%) High: 265 (32.5%)	$X^2 = 0.7$, df = 1, p = 0.390
Baseline GAD-7 score	14.3 ± 4.9	13.4 ± 5.1	14.1 ± 5.0	F(1, 1305) = 5.9, p = **0.015**
Baseline presence of comorbid PTSD[1]	No: 376 (35.7%) Yes: 677 (64.3%)	No: 129 (52.9%) Yes: 115 (47.1%)	No: 505 (38.9%) Yes: 792 (61.1%)	$X^2 = 24.5$, df = 1, p = **7.285×10^{-7}**
Baseline number of drinks per week[1]	3.3 ± 7.5 (n = 1060)	2.5 ± 4.9 (n = 246)	3.1 ± 7.0 (n = 1306)	F(1, 1304) = 2.8, p = **0.096**
Baseline at-risk drinking[1]	No: 835 (78.8%) Yes: 225 (21.2%)	No: 200 (81.3%) Yes: 46 (18.7%)	No: 1035 (79.2%) Yes: 271 (20.8%)	$X^2 = 0.8$, df = 1, p = 0.379
Baseline cannabis use[1]	No: 821 (77.5%) Yes: 239 (22.5%)	No: 191 (77.6%) Yes: 55 (22.4%)	No: 1012 (77.5%) Yes: 294 (22.5%)	$X^2 = 0.004$, df = 1, p = 0.949
Baseline drug use (other than cannabis or alcohol)[1]	No: 1049 (99.0%) Yes: 11 (1.0%)	No: 244 (99.2%) Yes: 2 (0.8%)	No: 1293 (99.0%) Yes: 13 (1.0%)	$X^2 = 0.1$, df = 1, p = 0.749
Baseline physical health[1]	35.1 ± 12.9 (n = 1060)	40.3 ± 13.5 (n = 245)	36.1 ± 13.1 (n = 1305)	F (1, 1303) = 31.9, **p = 2.0×10^{-8}**

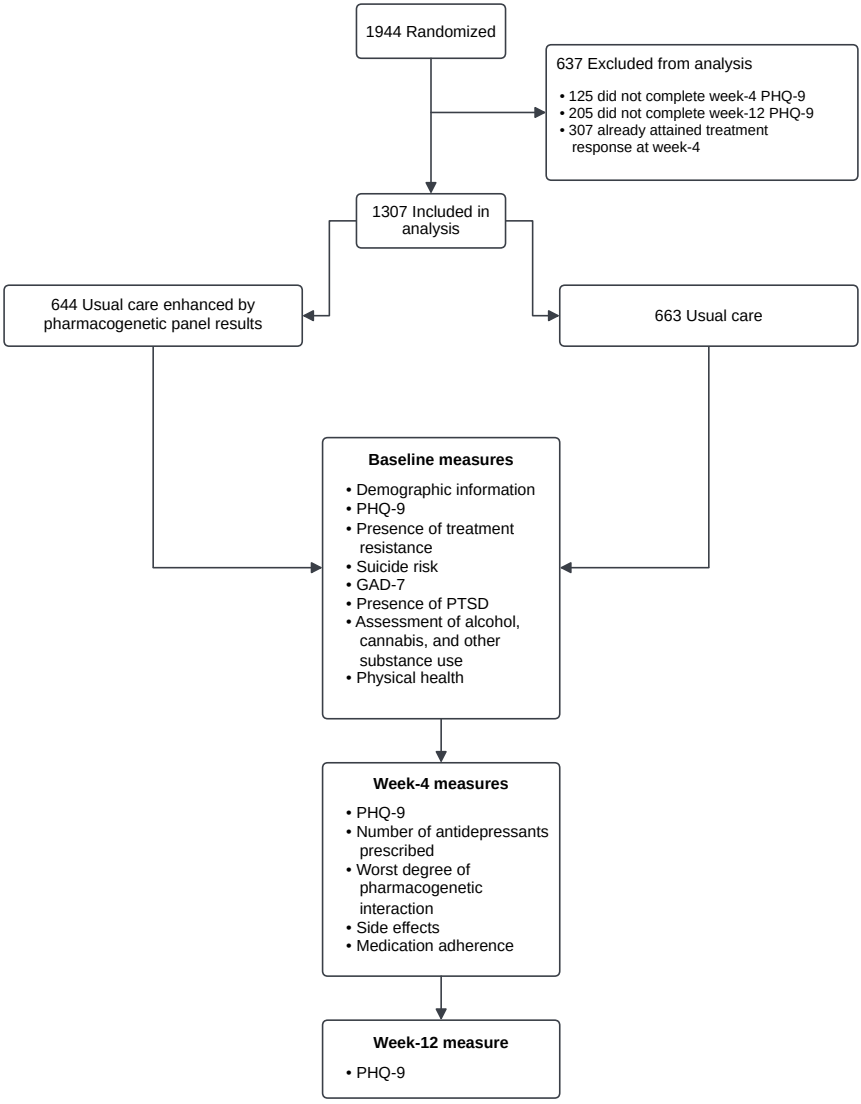
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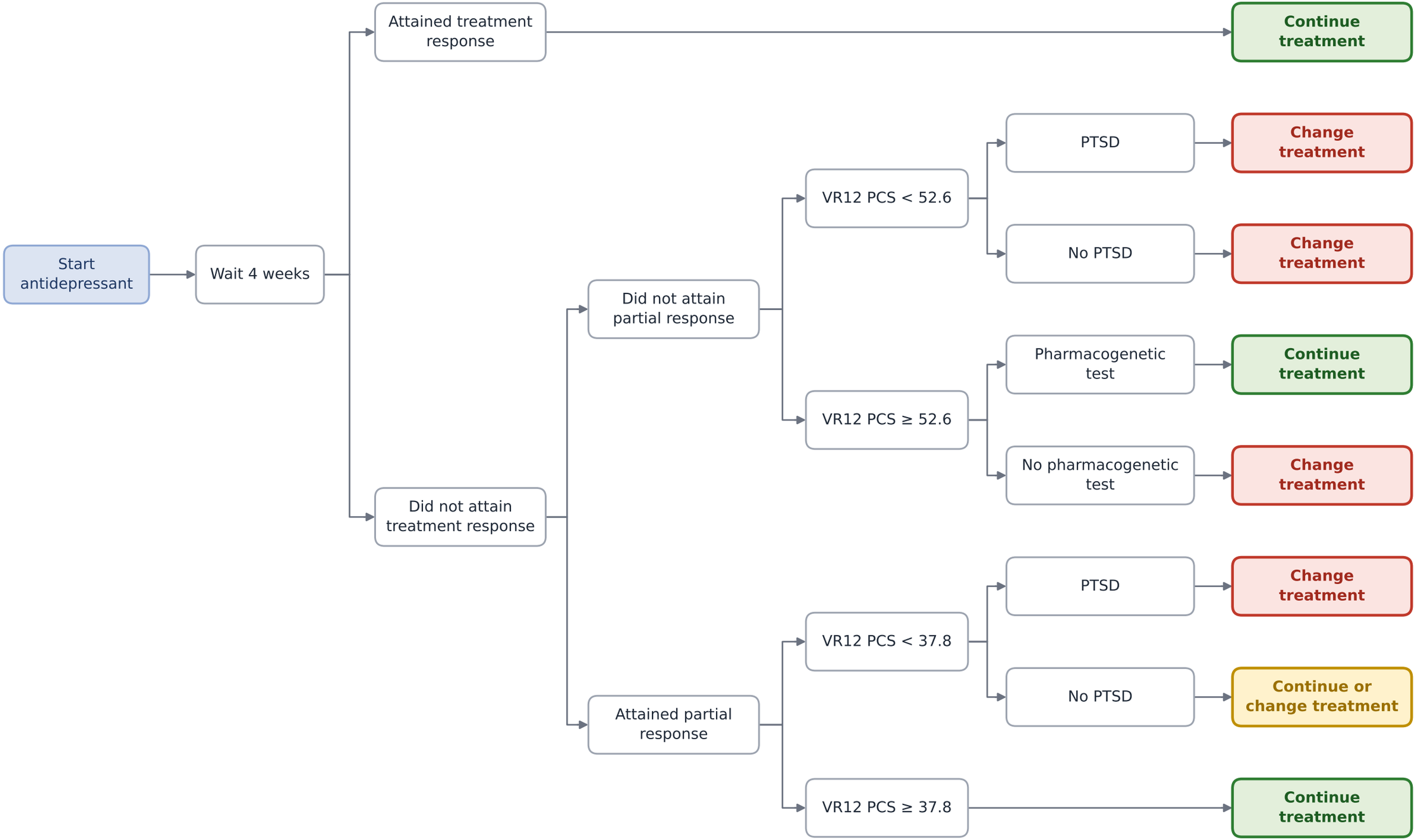
Week-4 potential predictors				
Response at week-4: none vs. partial	None: 830 (78.2%) Partial: 231 (21.8%)	None: 132 (53.7%) Partial: 113 (45.9%)	None: 962 (73.6%) Partial: 345 (26.4%)	$X^2 = 62.0$, df = 1, p = $\mathbf{3.4 \times 10^{-15}}$
Number of anti-depressants prescribed at week-4[1]	1.3 ± 0.5 (n =824)	1.3 ± 0.6 (n = 201)	1.3 ± 0.5 (n = 1025)	F(1, 1023) = 0.7, p = 0.403
Worst degree of drug-gene interaction of the prescribed antidepressants at week-4[1,3]	Green: 320 (38.9%) Yellow: 353 (42.9%) Red: 150 (18.2%)	Green: 83 (41.3%) Yellow: 82 (40.8%) Red: 36 (17.9%)	Green: 403 (39.4%) Yellow: 435 (42.5%) Red: 186 (18.2%)	$X^2 = 0.4$, df = 2, p = 0.813
Any AE at week-4[1]	No: 347 (40.1%) Yes: 519 (59.9%)	No: 94 (45.9%) Yes: 111 (54.1%)	No: 441 (41.2%) Yes: 630 (58.8%)	$X^2 = 2.3$, df = 1, **p = 0.130**
Severity of headache as AE at week-4[1]	0.4 ± 0.9 (n = 866)	0.4 ± 0.8 (n = 205)	0.4 ± 0.9 (n = 1071)	F(1, 1069) = 0.7, p = 0.406
Severity of nausea as AE at week-4[1]	0.3 ± 0.6 (n = 866)	0.2 ±0.6 (n = 205)	0.2 ± 0.6 (n = 1071)	F(1, 1069) = 0.7, p = 0.390
Severity of diarrhea as AE at week-4[1]	0.2 ± 0.5 (n = 866)	0.2 ± 0.5 (n = 205)	0.2 ±0.5 (n = 1071)	F(1, 1069) = 0.2, p = 0.692
Severity of constipation as AE at week-4[1]	0.2 ± 0.5 (n = 866)	0.2 ±0.4 (n = 205)	0.2 ± 0.5 (n = 1071)	F(1, 1069) = 2.2, p = **0.137**

Severity of sexual dysfunction as AE at week-4[1]	0.7 ±1.1 (n = 866)	0.5 ± 1.0 (n = 205)	0.7 ±1.1 (n = 1071)	F(1, 1069) = 5.6, p = **0.018**
Severity of anxiety as AE at week-4[1]	0.02 ± 0.2 (n = 866)	0.01 ± 0.2 (n = 205)	0.02 ± 0.2 (n = 1071)	F(1, 1069) = 0.2, p = 0.636
Severity of irritability as AE at week-4[1]	0.04 ± 0.3 (n = 866)	0.03 ± 0.2 (n = 205)	0.04 ± 0.3 (n = 1071)	F(1, 1069) = 0.1, p = 0.734
Severity of fatigue as AE at week-4[1]	0.2 ± 0.6 (n = 866)	0.1 ± 0.5 (n = 205)	0.2 ± 0.6 (n = 1071)	F(1, 1069) = 2.0, p = **0.162**
Total AE score at week-4[1]	2.0 ± 2.4 (n = 866)	1.6 ± 2.0 (n = 205)	2.0 ± 2.3 (n = 1071)	F(1, 1069) = 6.6, p = **0.011**
Adherent with anti-depressant at week-4[1]	No: 156 (16.4%) Yes: 795 (83.6%)	No: 25 (11.2%) Yes: 199 (88.8%)	No: 181 (15.4%) Yes: 994 (84.6%)	X^2 = 3.8, df = 1, **p = 0.051**

Footnotes: [1] Indicates when n's of subgroups do not add to column n. [2]Statistics presented show the result of chi-square analysis for categorical variables and one-way ANOVA for continuous variables comparing week-12 non-responders vs. responders. P values for the 14 variables that were selected as potential predictors for the decision tree are bolded. [3]Potential psychotropic drug-gene interactions and suggested clinical management were categorized as green (no interactions none; use as directed), yellow (moderate drug interactions; use with caution), or red (substantial drug interactions; use with increased caution and more frequent monitoring).

Abbreviations: Generalized Anxiety Disorder – 7 items (GAD-7); Patient Health Questionnaire – 9 items (PHQ-9); Post-Traumatic Stress Disorder (PTSD); PRIME: Precision Medicine in Mental Health Care randomized controlled trial


1944 Randomized
637 Excluded from analysis
• 125 did not complete week-4 PHQ-9
• 205 did not complete week-12 PHQ-9
• 307 already attained treatment response at week-4
1307 Included in analysis
644 Usual care enhanced by pharmacogenetic panel results
663 Usual care
Baseline measures
• Demographic information
• PHQ-9
• Presence of treatment resistance
• Suicide risk
• GAD-7
• Presence of PTSD
• Assessment of alcohol, cannabis, and other substance use
• Physical health
Week-4 measures
• PHQ-9
• Number of antidepressants prescribed
• Worst degree of pharmacogenetic interaction
• Side effects
• Medication adherence
Week-12 measure
• PHQ-9


Start antidepressant
Wait 4 weeks
Attained treatment response
Continue treatment
Did not attain treatment response
Did not attain partial response
VR12 PCS < 52.6
PTSD
Change treatment
No PTSD
Change treatment
VR12 PCS ≥ 52.6
Pharmacogenetic test
Continue treatment
No pharmacogenetic test
Change treatment
Attained partial response
VR12 PCS < 37.8
PTSD
Change treatment
No PTSD
Continue or change treatment
VR12 PCS ≥ 37.8
Continue treatment

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