The clinical utility of combinatorial pharmacogenomic testing for patients with depression: a meta-analysis

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Aim: To perform a meta-analysis of prospective, two-arm studies examining the clinical utility of using the combinatorial pharmacogenomic test, GeneSight Psychotropic, to inform treatment decisions for patients with major depressive disorder (MDD). **Patients & methods:** The pooled mean effect of symptom improvement and pooled relative risk ratio (RR) of response and remission were calculated using a random effect model. **Results:** Overall, 1556 patients were included from four studies, with outcomes evaluated at week 8 or week 10. Patient outcomes were significantly improved for patients with MDD whose care was guided by the combinatorial pharmacogenomic test results compared with unguided care (symptom improvement $\Delta = 10.08\%$, 95% CI: 1.67–18.50; $p = 0.019$; response RR = 1.40, 95% CI: 1.17–1.67; $p < 0.001$; remission RR = 1.49, 95% CI: 1.17–1.89; $p = 0.001$). **Conclusion:** GeneSight Psychotropic guided care improves outcomes among patients with MDD.

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Achieving response and remission is the goal of treating any mental health disorder. Unfortunately, patients suffering from major depressive disorder (MDD) have only a 50% chance of reaching a clinically significant response with their first antidepressant medication, with even fewer reaching remission [1]. The rates of remission and response continue to decrease with each subsequent medication trial, which can lead to further challenges in treating depression [2]. Difficult-to-treat depression culminates in significant personal, financial and socioeconomic challenges that generate a great burden on the economy due to missed work, and decreases in productivity and quality of life [3]. Therefore, better tools are needed to more quickly help patients achieve clinical remission.

One promising option is the use of pharmacogenomics to guide treatment selection for patients with MDD [4,5] and other psychiatric disorders [6,7]. Pharmacogenomics is an evaluation of how drug tolerability and efficacy is affected by variants in pharmacokinetic and pharmacodynamic genes (gene–drug interactions) [8]. Pharmacokinetic genes are responsible for coding proteins that metabolize medications and pharmacodynamic genes code for proteins involved in medication effect. Historically, genetic variants were analyzed on an individual gene basis to determine possible gene–drug interactions. For example, CYP450 2D6 is often evaluated to determine whether there are any gene–drug interactions affecting the metabolism of the tricyclic antidepressant nortriptyline [9]. However, it is now well known that medications may be affected by more than one pharmacokinetic and/or pharmacodynamic gene [10].

The National Institutes of Health has funded the Clinical Pharmacogenomics Implementations Consortium (CPIC) to write pharmacogenomics guidelines based on systematic reviews performed by subject matter experts [11]. Most studies have examined the impact of one gene, usually within the CYP450 family, on one drug [12]. However, there are some instances where CPIC guidance cites multiple genes for a single medication. For example, CPIC provides a detailed dosing guidance and algorithm for warfarin that includes the genotypes of CYP2C19 and

VKORC1, two pharmacokinetic genes involved in warfarin metabolism [13]. CPIC also provides guidance for selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants based on the genotypes of CYP2D6 and CYP2C19. Although there is not clear CPIC guidance for SSRI prescribing when there is variation in both genes [10,14], some commercial pharmacogenomic tests provide guidance by using algorithms to weigh and combine the effects of multiple variants and genes.

There is a growing body of literature on the use of pharmacogenomics in MDD; however, there are mixed results regarding the utility of this testing. While randomized controlled trials (RCTs) are considered the gold standard to evaluate the effectiveness of a test, there may be concerns regarding reproducibility, bias and study limitations that can affect the quality of evidence [15,16]. This is particularly relevant in pharmacogenomic testing in depression, where trial results vary drastically depending on which specific test was utilized, the study population and patient outcomes evaluated. By combining similar studies into a meta-analysis, potential biases from individual studies can be minimized to provide more robust evidence. The importance of meta-analyses has been recognized by evidence frameworks such as Grading of Recommendations Assessment, Development and Evaluations and a hierarchy of evidence has been established using this or other frameworks [15,16]. For example, the Canadian Network for Mood and Anxiety Treatments [17] and the Agency for Healthcare Research and Quality [18] consider a meta-analysis as the highest level of evidence. Data produced from such studies are therefore an important component in informing practice guidelines.

Recently, Bousman *et al.* and Rosenblat *et al.* have published meta-analyses examining outcomes among patients with MDD who had access to the results of various commercial pharmacogenomic tests, with Bousman *et al.* including only RCTs [19,20]. Both meta-analyses found a significant association between the pharmacogenomics guided treatment and remission among patients with MDD [19,20]. However, both reports acknowledged the potential impact of differences between the pharmacogenomic tests, which may limit the generalizability of the meta-analysis findings [19,20]. The utility of each clinical pharmacogenomic test should depend on which genes are included, how genotypes and phenotypes are assigned, whether a single or combinatorial gene approach is used and the specific combinatorial algorithm utilized. As a result, the different tests are not comparable [21] and the results of a meta-analysis of the collective utility of pharmacogenomic testing do not directly reflect on the utility of any single test.

Here, we present a meta-analysis of four prospective, controlled clinical studies that evaluated the clinical utility of the combinatorial pharmacogenomic test GeneSight Psychotropic among patients with MDD who had at least one prior medication failure. All four studies evaluated multiple measures of patient outcomes (remission, response and symptom improvement) using the 17-item Hamilton Depression Rating Scale (HAM-D17) among patients whose medication selection was informed by the combinatorial pharmacogenomic test results (guided care) compared with unguided care. Analyses were also performed according to the study type, with a separate evaluation of all RCTs.

Patients & methods

Selection criteria

We utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [22]. Two reviewers (T Al Habbab and H Johnson) both independently searched MEDLINE/PubMed for published reviews, meta-analyses and primary studies evaluating the impact of pharmacogenomic testing on outcomes for patients with MDD. Search terms included “pharmacogenomics”, “guided”, “study”, “antidepressant”, “depression” and “clinician”.

All identified reports were screened for inclusion based on two rounds of review. The first round of review included an evaluation of the abstract to identify studies that utilized the GeneSight Psychotropic test. The second round was based on evaluation of the following inclusion criteria via full-text reviews: two-arm, prospective studies evaluating the clinical utility of GeneSight Psychotropic; including patients ≥ 18 years of age diagnosed with MDD and assessing depressive symptom improvement, response and/or remission using HAM-D17. Both open-label and RCTs were eligible for inclusion. The Risk of Bias Assessment Tool from Cochrane Collaboration, was used to evaluate a possible source of bias for all included articles [23].

Statistical analysis

Symptom improvement from baseline was measured by the percentage change in HAM-D17 from baseline. Mean percentage of symptom improvement, sample size for each treatment arm and pairwise comparison p-values from

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for identifying clinical studies included in this meta-analysis.

each study were used for the meta-analysis. For response and remission, the relative risk ratio (RR) of guided care to the unguided care at week 8 or week 10 with 95% lower and upper confidence intervals was determined for each study and was used for analyses. Meta-analyses were performed for all four studies, two open-label studies and two RCTs. To assess the influence of any given study, each study was omitted and meta-analyses were rerun to determine their influence on the pooled effect size.

The pooled mean effect of symptom improvement and pooled RR of response and remission for all four studies and omitting one study were calculated using a random effect model. The random effects model was utilized to address differences based on study design (open-label and RCTs) and between-study and within-study sampling errors. The pooled mean effect of symptom improvement and pooled RR of response and remission for the two open-label studies and two RCTs were calculated using a fixed effect model. The fixed effect model is appropriate as the study design and types were the same and were to estimate the same treatment effect. Heterogeneity in effect sizes across studies were tested using the Q-statistic and its magnitude was measured by the I^2 statistic ($I^2 = 25\%$, small heterogeneity; 50% , moderate heterogeneity; 75% , high heterogeneity) [18]. Comprehensive meta-analysis V2 was used for all meta-analyses.

Results

Description of included studies

In total, the systematic Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) literature review identified ten studies that met the search criteria (Figure 1). After the first round of review, three studies that did not evaluate GeneSight Psychotropic were excluded (Supplementary Table 1). Two additional studies were excluded in the second round of review as they did not meet the inclusion criteria (Supplementary Table 1). The remaining five publications were appropriate for inclusion (Figure 1 & Table 1). Two of these publications reported on open-label trials (Hall-Flavin *et al.*, 2012 and 2013 [30,31]) and two reported on RCTs (Winner *et al.* and Greden *et al.* [27,32]). A pooled analysis (Altar *et al.* [33]) of the two open-label trials and the RCT by Winner *et al.*

Table 1. Description of the five publications on four studies evaluating the clinical utility of GeneSight Psychotropic in guiding treatment selection for patients with major depressive disorder.

Study (year)	Study design	Eligibility	Baseline cohort characteristics [†]	Target genes	Outcomes reported	Potential sources of bias [‡]	Ref.
Hall-Flavin <i>et al.</i> (2012)	<ul style="list-style-type: none"> • 8 week, prospective, open-label study • Two arms: guided care vs unguided care • Assessment points: baseline, 2, 4 and 8 weeks 	Inclusion: <ul style="list-style-type: none"> • Primary diagnosis of MDD (DSM-IV criteria) • HAM-D17 score ≥ 14 Exclusion: <ul style="list-style-type: none"> • Diagnosis of bipolar disorder type I, schizophrenia and schizo-affective disorder 	Guided care (n = 25 baseline; 22 analyzed) vs unguided care (n = 26 baseline; 22 analyzed) <ul style="list-style-type: none"> • Age (years): 42.1 vs 42.6 (ns) • Sex (% female): 54.5 vs 54.5 (ns) • Baseline HAM-D17: specific values not reported; Altar <i>et al.</i> states 20.6 vs 18.4 (ns) • Failed medication trials: 6.0 vs 6.7 (ns) 	CYP1A2, CYP2C19, CYP2D6, SLC6A4, HTR2A	Symptom improvement	Industry funded, recruitment [§] , patients and clinicians unblinded	[30]
Hall- Flavin <i>et al.</i> (2013)	<ul style="list-style-type: none"> • 8 week, prospective, open-label study • Two arms: guided care vs unguided care • Assessment points: baseline, 2, 4 and 8 weeks 	Inclusion: <ul style="list-style-type: none"> • ≥ 18 years of age • Diagnosed with MDD (DSM-IV) • HAM-D17 score ≥ 14 Exclusion: <ul style="list-style-type: none"> • Diagnosis of bipolar type I, schizophrenia, or schizo-affective disorder 	Guided care (n = 114 baseline; n = 72 week 8) vs unguided care (n = 113 baseline; 93 week 8) <ul style="list-style-type: none"> • Age (years): 41 vs 44 (ns) • Sex (% female): 69.3 vs 77 (ns) • Baseline HAM-D17: 23 vs 22.5 (ns) • Failed medication trials: 3.6 vs 4.7 (p = 0.021) 	CYP1A2, CYP2C19, CYP2D6, SLC6A4, HTR2A	Symptom improvement, response, remission	Industry funded, recruitment [§] , patients and clinicians unblinded	[31]
Winner <i>et al.</i> (2013)	<ul style="list-style-type: none"> • 10 week, prospective, patient and rater blinded, RCT • Two arms: guided care (GeneSight) vs unguided care (TAU) • Assessment points: baseline, 4, 6 and 10 weeks 	Inclusion: <ul style="list-style-type: none"> • Diagnosed with MDD or DDNOS • HAM-D17 score ≥ 14 Exclusion: <ul style="list-style-type: none"> • Diagnosis of bipolar disorder (any type), schizophrenia, or schizo-affective disorders • Active diagnosis of substance abuse or dependence 	Guided care (n = 26 baseline; 25 week 10) vs unguided care (n = 25 baseline; 24 week 10) <ul style="list-style-type: none"> • Age (years): 50.6 vs 47.8 (ns) • Sex (% female): 69 vs 92 (p = 0.04) • Ethnicity (% Caucasian): 96 vs 100 (ns) • Baseline HAM-D17: specific values not reported; Altar states 21.6 vs 21.1 (ns) • Failed medication trials: 4.3 vs 4.5 (ns) 	CYP1A2, CYP2C19, CYP2D6, SLC6A4, HTR2A	Symptom improvement, response, remission	Industry funded, recruitment [§] , treating clinician not blinded	[32]
Altar <i>et al.</i> (2015)	<ul style="list-style-type: none"> • Meta-analysis of Hall-Flavin 2012, Hall-Flavin 2013 and Winner 2013 	NA	Guided care (n = 119) vs unguided care (n = 139) <ul style="list-style-type: none"> • Baseline HAM-D17: 22.4 vs 21.5 (ns) 	NA	Symptom improvement, response, remission	NA	[33]
Greden <i>et al.</i> (2019)	<ul style="list-style-type: none"> • 8 week, prospective, patient and rater blinded, RCT; open-label extension through 24 weeks. • Two arms: guided care vs unguided care (TAU) • Assessment points: blinded: baseline, 4 and 8 weeks; unblinded: 12 and 24 weeks 	Inclusion: <ul style="list-style-type: none"> • ≥ 18 years of age • Diagnosed with MDD (≥ 11 on QIDS-C16 and QIDS-SR16) • Failed ≥ 1 psychotropic medication on the GeneSight Psychotropic test in the current depressive episode Exclusion: <ul style="list-style-type: none"> • Significant suicidal risk • Some severe co-occurring psychiatric or cognitive disorders • Unstable or significant medical conditions 	ITT: guided care (n = 760) vs unguided care (n = 781) <ul style="list-style-type: none"> • Age (years): 47.3 vs 48 (ns) • Sex (% female): 71.6 vs 68.5 (ns) • White (%) : 80 vs 82.6 (ns) • Baseline HAM-D17: 20.49 vs 20.74 (ns) • Failed medication trials: 3.44 vs 3.52 (ns) 	CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, SLC6A4, HTR2A	Symptom improvement, response, remission	Industry funded, recruitment [§] , treating clinician not blinded	[27]

[†] Percentages or means are reported for all cohort characteristics.[‡] Categories from the Risk of Bias Assessment Tool from Cochrane Collaboration that received a rating of 'high' are listed.[§] Potential source of recruitment bias stems from subject referral for the study by the treating clinician.

DDNOS: Dissociative disorder not otherwise specified; DSM: Diagnostic and Statistical Manual of Mental Disorders; HAM-D17: 17-item Hamilton depression rating scale; ITT: Intent-to-treat; MDD: Major depressive disorder; NA: Not applicable; ns: Not significant; RCT: Randomized controlled trial; TAU: Treatment as usual.

also met the inclusion criteria because additional patient outcome information was included for the cohort in the Hall-Flavin *et al.* (2012) trial and Winner *et al.* (2013) RCT that was not published in the primary report; however, the publication was not considered a separate study because it included the same patient populations as Hall-Flavin

et al. (2012) and Winner *et al.* (2013, [32]). As such, data from four unique studies reported in five publications were included in the meta-analysis.

All studies utilized the same combinatorial pharmacogenomic test, though the specific genes included in the test were different between some studies (Table 1). The primary objective in all included studies was an assessment of patient outcomes using HAM-D17. For most studies, patient outcomes were evaluated at week 8, and Winner *et al.* assessed patient outcomes at week 10. The four studies were prospectively enrolled and included a combinatorial pharmacogenomic guided care arm and an unguided care arm. Patients in the unguided care arm for all four studies received active treatment for their MDD that was not guided by the results of pharmacogenomic testing. A total of 1556 eligible subjects from the four unique clinical studies were examined. All four studies had approximately even distribution between the guided care and unguided care arms (Table 1).

Risk of bias

The four studies assessed were subject to multiple sources of bias (Table 1). The risk of bias for all the studies included here have been previously reported as part of the meta-analyses by Bousman *et al.* and/or Rosenblat *et al.* [19,20]. As the same framework was utilized here, our findings did not differ from what has been previously reported. In brief, selection, detection, attrition and reporting biases were all low for the two RCTs and the two open-label trials. The fact that treating physicians in both RCTs were not blinded to study arm resulted in high performance bias for these trials. Neither physicians nor patients were blinded to treatment group in the open-label studies. There was high recruitment bias for the open-label trials and RCTs, as physicians could refer subjects to be included in the trial. In addition, there was also a potential bias to these studies due to industry sponsorship and involvement in study design, execution and analysis.

Symptom improvement

The primary end point of all four studies was symptom improvement, measured as percent change from baseline HAM-D17 score to week 8 (Hall-Flavin *et al.*, 2011 and 2012; Greden *et al.*) or 10 (Winner *et al.*). The heterogeneity in effect size across the four studies was significant, but moderate ($Q = 10.62$; $p = 0.014$; $I^2 = 71.75$; Figure 2A). The random-effects model suggests that symptom improvement was significantly better when the combinatorial pharmacogenomic test results were available to the physician, with HAM-D17 scores decreasing an additional 10.08% (95% CI: 1.67–18.50; $p = 0.019$) from baseline to week 8/10 for guided care versus unguided care (Figure 2A). Overall, the guided care had a 33.8% reduction in HAM-D17 score while the unguided care had a 23.7% reduction, representing a 43% improvement over the unguided care. Removal of either of the open-label studies from the analysis showed that symptom improvement was greater for the guided care versus unguided care, but the difference was no longer significant (Hall-Flavin *et al.*, 2012; $\Delta = 9.54$, 95% CI: -1.09–20.17; $p = 0.079$ and Hall-Flavin *et al.*, 2013; $\Delta = 5.76$, 95% CI: -0.17–11.69; $p = 0.057$; Supplementary Figure 1A).

When the studies were grouped by trial design, symptom improvement was significantly larger for guided care compared with unguided care for the open-label studies ($\Delta = 15.5$, 95% CI: 8.72–22.29; $p < 0.001$) and the RCTs ($\Delta = 3.44\%$, 95% CI: 0.06–6.83; $p = 0.046$; Figure 3A). The magnitude of the difference was lower for the RCTs.

Response

Overall response based on HAM-D17 was also evaluated for all four studies, defined as at least a 50% reduction in HAM-D17 score from baseline to week 8/10. The effect size of response was consistent across all four studies ($Q = 2.43$; $p = 0.489$, $I^2 = 0.000$; Figure 2B). The pooled RR suggests that the guided care arm had a 40% higher response rate compared with the unguided arm (RR = 1.40, 95% CI: 1.17–1.67; $p < 0.001$; Figure 2B). The RR for response was relatively constant when each of the trials was systematically removed from the analysis, with the exception Greden *et al.* (RR = 1.71, 95% CI: 1.17–2.49; $p = 0.005$); however, the RR for response remained significant regardless of which study was omitted (Supplementary Figure 1B).

Response was significantly higher among patients in the guided care arm for both the open-label trials (RR = 1.72, 95% CI: 1.11–2.67; $p = 0.016$) and RCTs (RR = 1.34, 95% CI: 1.10–1.62; $p = 0.004$, respectively; Figure 3B).

Remission

All four studies also evaluated remission, defined as HAM-D17 scores reaching ≤ 7 . The effect size of remission was consistent across the four studies ($Q = 0.539$; $p = 0.910$, $I^2 = 0.000$; Figure 2C). The pooled RR suggests that patients who received combinatorial pharmacogenomic-guided care achieved 49% higher remission compared

Figure 2. Forest plot of random-effects meta-analysis of four prospective, two-arm studies that examined the clinical utility of GeneSight Psychotropic in guiding treatment decisions for patients with major depressive disorder. (A) Average difference in symptom improvement, (B) RR for response and (C) RR for remission between guided and unguided care. Circle size indicates weight in overall analysis. RR: Relative risk ratio.

unguided care (RR = 1.49, 95% CI: 1.17–1.89; $p = 0.001$; Figure 2C). The RR for remission was relatively constant when each of the trials was systematically removed from the analysis, though remission was not significantly different when Greden *et al.* was removed ($p = 0.075$; Supplementary Figure 1C).

The open-label studies did not exhibit significantly higher remission rates among the guided care arm compared with the unguided care arm (RR = 1.47, 95% CI: 0.89–2.41; $p = 0.130$; Figure 3C). However, the rate of remission in the RCTs was 49% higher for guided care compared with unguided care (RR = 1.49, 95% CI: 1.14–1.96; $p = 0.004$).

Figure 3. Forest plot of fixed-effects meta-analysis for the open-label and randomized controlled trials. (A) Average difference in symptom improvement, **(B)** RR for response and **(C)** RR for remission between guided and unguided care. Circle size indicates weight in overall analysis. RCT: Randomized controlled trial; RR: Relative risk ratio.

Discussion

As pharmacogenomic testing has emerged as a data-driven solution to improve treatment of MDD, it is necessary to ensure that utilization of these tests to inform medication selection is safe and effective. Recent meta-analyses have been performed for pharmacogenomic tests as a class [19,20], reporting that remission is significantly associated with pharmacogenomic-guided care. However, the generalizability of these findings is inherently limited due to differences among the pharmacogenomic tests that fundamentally alter the information provided regarding gene–drug interactions. This is apparent in the substantial differences in the individual studies and in the meta-analyses themselves. Although meta-analyses provide a very high level of evidence regarding the utility of pharmacogenomic

testing, a more appropriate approach is to perform meta-analyses for individual pharmacogenomic tests. Here, we performed a meta-analysis for studies reporting on a single combinatorial pharmacogenomic test, GeneSight Psychotropic, to provide more informative results regarding the clinical utility of that test.

This meta-analysis included prospectively enrolled, two-arm trials that utilized the combinatorial pharmacogenomic test to inform medication selection for patients with MDD who had failed at least one prior medication. Overall, these data show that patient care guided by this combinatorial pharmacogenomic test resulted in significantly better symptom improvement, response rates and remission rates compared with unguided care. Importantly, there was a very low degree of heterogeneity for response and remission and moderate heterogeneity for symptom improvement across all four studies, indicating that it is appropriate to combine these studies. As meta-analyses are recognized as the highest level of evidence by many organizations, this analysis provides important additional support that that difficult-to-treat patients with MDD can benefit from this combinatorial pharmacogenomic test [24–26]. It is important to note that there is overlap between the studies included in this meta-analysis and the two recent meta-analyses from Rosenblat *et al.* [20] and Bousman *et al.* [19] that reported on pharmacogenomics as a class. As such, care should be taken to not overinterpret the body of evidence available supporting pharmacogenomic testing as a class. However, the evidence provided for the combinatorial pharmacogenomic test in the meta-analysis presented here does provide strong evidence of the utility of that individual test.

The data presented here also provides additional insights into the impact of the placebo effect of pharmacogenomic testing and how that may impact the interpretation of clinical utility data. In the subanalyses by trial type, the magnitude of the difference in symptom improvement between arms decreased for the RCTs compared with the open-label trials. In addition, there was large variation in the difference between arms when each study was systematically removed, resulting in a moderate, but significant, degree of heterogeneity for the symptom improvement end point across the four studies. This heterogeneity may be unexpected for studies utilizing the same patient population and test; however, it is consistent with a placebo effect resulting in increased symptom improvement when the patient is aware that they are getting personalized genetic results. This sort of placebo effect was also found by Rosenblat *et al.*, and was determined to be due to expectancy bias [20]. However, there was much less variation in the RR for response in the subanalyses by trial design and with systematic removal of each study presented here. This was even more apparent for remission, where there was virtually no difference in any of the subanalyses. This was also reflected in the heterogeneity analysis, which showed highly consistent results between studies for response and remission. Collectively, these data indicate that response and remission are more insulated from placebo effects, likely because they are more difficult to achieve. As such, the significant improvement in patient outcomes achieved with combinatorial pharmacogenomic-guided care represents a true improvement based on utilizing the test results to inform treatment selection.

The data included here provides continued support of the clinical utility of this combinatorial pharmacogenomic test in informing treatment selection for patients with MDD. This builds upon the recently reported findings from the Genomics Used to Improve Depression Decisions (GUIDED) RCT from Greden *et al.* [27]. GUIDED is the largest RCT performed to date examining the clinical utility of pharmacogenomic testing in mental health and reported significant improvements in response and remission rates. However, there have been several criticisms of the trial design. This includes concerns regarding the duration of the blinded period; however, the 8-week blinded period is consistent with US FDA draft guidance on studies of short-term treatment for MDD (treatment of a depressive episode), which indicates that ‘antidepressants in established classes (e.g., SSRIs, serotonin-norepinephrine reuptake inhibitor [SNRIs]) typically need studies of 6–8 weeks duration to demonstrate efficacy’ [28].

There have also been concerns that the treating clinician was not blinded in the GUIDED trial and for other RCTs on pharmacogenomic testing. It has been proposed that the lack of clinician blinding may impart a placebo effect to the patients based on physician expectation of success. While this may be a limitation, an ethical and viable alternative is not obvious [19]. For the combinatorial pharmacogenomic test evaluated here, clinician judgement is a critical component of patient care to inform possible treatment decisions including adding a medication, dropping a medication and/or changing the dose of an existing medication. Although it is difficult to assess whether there is any physician placebo effect in GUIDED, the robust remission end point is likely insulated from placebo effects, as discussed previously. As such, the significant findings for remission in the GUIDED trial and in this meta-analysis provide evidence of the clinical utility of GeneSight Psychotropic even in the absence of clinician blinding.

In addition to evidence of clinical utility, it is important that pharmacogenomic tests be also supported by robust evidence of analytical validity, clinical validity and economic utility in order to make them appropriate for clinical use [29]. Several prospective and retrospective studies have demonstrated the clinical validity and utility of this

combinatorial pharmacogenomic test in patients with MDD who have failed at least one medication trial [30–35]. This includes five prospective clinical trials in two countries that were performed in collaboration with multiple academic centers [27,30–32,35], four of which were included in this study. In addition, the analytical validity [36] and cost–effectiveness [37–40] of the GeneSight Psychotropic test have also been demonstrated.

Limitations

This meta-analysis had some limitations. All of the included studies were industry-funded, potentially resulting in bias. However, non-industry trials of this sort have yet to be performed and it is therefore unknown what potential bias this may confer [17]. This analysis is also limited by a lack of ethnic diversity among the study populations, with the majority of patients being Caucasian. In addition, only one database (PubMed/Medline) was searched. Finally, data from two different types of studies were combined for the overall meta-analysis: open-label trials and RCTs. However, all studies had a similar study design and used the same primary outcomes and scales, which allowed for this combination. This sort of meta-analysis design is not novel, as the recent Rosenblat *et al.* meta-analysis also combined open-label trials and RCTs [20]. Combining these data provides important insight into the utility in real-world settings (open-label) as well as blinded RCTs.

Conclusion & future perspective

Although previous meta-analyses have demonstrated the utility of pharmacogenomic testing, the generalizability of those findings are limited by substantive differences in the individual pharmacogenomic tests. This meta-analysis of four studies reporting on the clinical utility of GeneSight Psychotropic testing demonstrates that utilization of this pharmacogenomic test to inform treatment decisions for patients with MDD with at least one prior medication failure is associated with improved patient outcomes compared with unguided care. This was true for all patient outcomes evaluated, including symptom improvement, response and remission. In addition, a separate analysis of the two RCTs that have evaluated the clinical utility of this test showed consistent results, with significant findings across all evaluated patient outcomes.

Summary points

- Up to 50% of patients with major depressive disorder do not reach clinical response during their first medication trial.
- Pharmacogenomic testing is a possible solution to improve treatment for depression by supporting data-driven treatment recommendations.
- There are many available pharmacogenomic tests, each with different testing approaches and varying levels of evidence supporting their clinical utility.
- Meta-analyses are recognized as the highest level of evidence by organizations such as the Canadian Network for Mood and Anxiety Treatments, and the Agency for Healthcare Research and Quality.
- Because it is not appropriate to evaluate the collective impact of pharmacogenomics as a class due to the significant differences between available tests, we performed a meta-analysis of the available evidence for the GeneSight Psychotropic test.
- Both open-label and randomized, controlled trials were included, with some potential sources of bias (i.e., industry sponsorship and potential recruitment bias).
- There was moderate heterogeneity between the studies for symptom improvement, but little to no heterogeneity for the response and remission end points.
- There was a significant improvement for patients who received GeneSight Psychotropic-guided care compared with unguided care for all outcomes evaluated (symptom improvement, response and remission).
- All outcomes evaluated were significantly improved when just the two randomized, controlled trials were evaluated.
- Overall, the meta-analysis presented here provides robust evidence of the clinical utility of GeneSight Psychotropic guided treatment for patients with major depressive disorder who have at least one prior medication failure.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pgs-2019-0157

Financial & competing interests disclosure

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