Does Pharmacogenomic Testing Improve Clinical Outcomes for Major Depressive Disorder?

A Systematic Review of Clinical Trials and Cost-Effectiveness Studies

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ABSTRACT

Objective: Pharmacogenomic testing has become scalable and available to the general public. Pharmacogenomics has shown promise for predicting antidepressant response and tolerability in the treatment of major depressive disorder (MDD). In theory, pharmacogenomics can improve clinical outcomes by guiding antidepressant selection and dosing. The current systematic review examines the extant literature to determine the impact of pharmacogenomic testing on clinical outcomes in MDD and assesses its cost-effectiveness.

Data Sources: The MEDLINE/PubMed and Google Scholar databases were systematically searched for relevant articles published prior to October 2015. Search terms included various combinations of the following: *major depressive disorder (MDD), depression, mental illness, mood disorder, antidepressant, response, remission, outcome, pharmacogenetic, pharmacogenomics, pharmacodynamics, pharmacokinetic, genetic testing, genome wide association study (GWAS), CYP450, personalized medicine, cost-effectiveness,* and *pharmacoeconomics.*

Study Selection: Of the 66 records identified from the initial search, relevant clinical studies, written in English, assessing the cost-effectiveness and/or efficacy of pharmacogenomic testing for MDD were included.

Data Extraction: Each publication was critically examined for relevant data.

Results: Two nonrandomized, open-label, 8-week, prospective studies reported overall greater improvement in depressive symptom severity in the group of MDD subjects receiving psychiatric care guided by results of combinatorial pharmacogenomic testing (GeneSight) when compared to the unguided group. One industry-sponsored, randomized, double-blind, 10-week prospective study reported a trend for improved outcomes for the GeneSight-guided group; however, the trend did not reach statistical significance. Another industry-sponsored, randomized, double-blind, 12-week prospective study reported a 2.5-fold increase in remission rates in the CNSDose-guided group ($P < .0001$). One naturalistic, unblinded, industry-sponsored study showed clinical improvement when pharmacogenomics testing guided prescribing; however, this study lacked a control group. A single cost-effectiveness study concluded that single gene testing was not cost-effective. Conversely, a separate study reported that combinatorial pharmacogenomic testing is cost-effective.

Conclusions: A limited number of studies have shown promise for the clinical utility of pharmacogenomic testing; however, cost-effectiveness of pharmacogenomics, as well as demonstration of improved health outcomes, is not yet supported with replicated evidence.

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Major depressive disorder (MDD) is a highly prevalent and chronic mental illness associated with significant disability, morbidity, and mortality.[1–3] The functional impairment associated with MDD has significant social and economic consequences globally.[4–6] Therefore, the effective treatment and prevention of MDD has been recognized internationally as a priority in health care research and delivery.[7]

The use of antidepressants to treat moderate to severe MDD is highly recommended by MDD treatment guidelines authored by international experts and other stakeholders.[8–10] According to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, approximately one-third of subjects with MDD will respond to the first guideline-informed antidepressant.[11,12] After multiple trials of mechanistically dissimilar antidepressants, approximately one-third of subjects with MDD fail to achieve remission from their acute episode. Variability in treatment response and tolerability is complex, with numerous contributing factors, including age, gender, diagnostic accuracy, drug-drug interactions, renal and hepatic function, medical and psychiatric comorbidity, treatment adherence, and other known and unknown genetic and environmental factors.[13,14] Recent genome-wide association studies (GWAS) have suggested the proportion of variance in antidepressant response explained by common genetic variation may be as high as 42%.[15]

At the current time, the selection of antidepressants in the treatment of MDD is largely based upon trial and error as first-line agents have been shown to be similarly efficacious in undifferentiated populations.[16] Insufficient outcomes observed with antidepressant therapy, as well as concerns related to the tremendous human and societal costs associated with MDD, provide the impetus for more "precision" and personalized-based approaches to antidepressant selection and sequencing. Clinicians and stakeholders yearn to identify the right treatment at the right dose for the right patient.

Recently, pharmacogenetic (ie, evaluating a single gene) and pharmacogenomic (ie, evaluating

multiple genes) testing have shown promise for informing selection of antidepressants.[17] Pharmacogenetic and pharmacogenomic testing have been developed to provide an a priori prediction of what medication may yield the highest likelihood of treatment response and/or the lowest risk of adverse events for a specific individual.[18] Toward this aim, pharmacogenomics may assess genetic factors impacting the variability in pharmacodynamics (ie, the action of the drug on the body; primarily evaluated through assessment of receptor and transporter function) and pharmacokinetics (ie, the action of the body on the drug; primarily evaluated through assessment of cytochrome P450 [CYP] enzyme activity).[18] Pharmacogenetic testing has proven to be helpful as a proof-of-concept in other fields of medicine, most notably in oncology, where genetic testing may directly dictate the selection of specific chemotherapy agents, thereby greatly improving outcomes in the treatment of cancer.[19] In psychiatry, pharmacogenetics is still in early development, however, has already been shown to be helpful in specific scenarios, such as HLA typing to predict the risk of severe adverse events (eg, Stevens-Johnson syndrome) to carbamazepine among Han Chinese patients.[20,21]

In theory, an understanding of an individual's pharmacodynamics and pharmacokinetics for specific antidepressants may enhance precision as it relates to prediction of treatment response and propensity for adverse events. Notwithstanding, empirical evidence is required to demonstrate that utilization of pharmacogenomic testing results in improved health outcomes among those with MDD and/or is a cost-effective intervention. Such evidence would be required prior to these tests being fully incorporated into (and paid for in) clinical practice.

The coprimary aims of the current systematic review are to determine, based on extant literature, whether it is empirically established that pharmacogenomics (1) is cost-effective and/or (2) improves consensually agreed upon therapeutic objectives in MDD. Toward these foregoing coprimary aims, we evaluate and synthesize results from published studies that have empirically evaluated pharmacogenomics and antidepressant selection/outcomes in adults with MDD. Of note, the current review does not evaluate the evidence for specific pharmacogenomic candidate genes or discuss specific polymorphisms, as several other authors have extensively reviewed this topic recently.[18,22–24]

Clinical Points

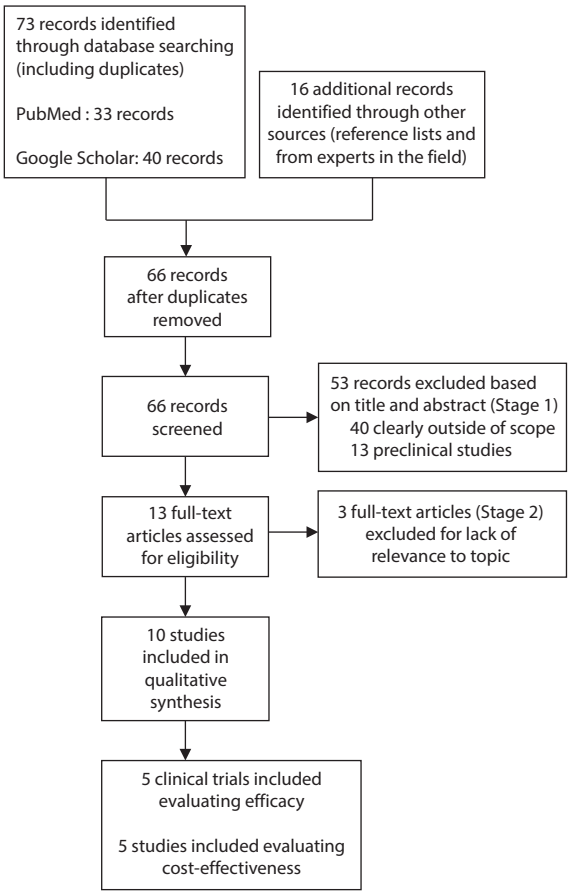
- Pharmacogenomic testing has become scalable and available to the general public; however, the benefits of testing remain unclear.
- Demonstration of improved health outcomes and cost-effectiveness of pharmacogenomics is not yet supported with replicated evidence.
- The ability of pharmacogenomics to improve remission and response rates to antidepressants therefore currently remains theoretical rather than evidence based.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines were followed for the current systematic review; however, the protocol for the current systematic review was not registered prior to conducting the review. MEDLINE/PubMed and Google Scholar databases were searched from inception through October 2015 for published reviews, meta-analyses, and primary studies evaluating the impact of pharmacogenomic testing on MDD treatment outcomes and its cost-effectiveness/cost-utility. Search terms included various combinations of the following: *major depressive disorder (MDD), depression, mental illness, mood disorder, antidepressant, response, remission, outcome, pharmacogenetic, pharmacogenomics, pharmacodynamics, pharmacokinetic, genetic testing, genome wide association study (GWAS), CYP450, personalized medicine, cost-effectiveness,* and *pharmacoeconomics*. Reference lists from identified articles were also manually searched for additional pertinent references. Google Scholar was used to identify articles that had cited the previously identified pharmacogenomic studies to identify additional potential articles of interest.

All identified articles were screened for inclusion in the current systematic review. Two rounds of screening were conducted: in Stage 1, all records from the initial search results were screened based on title and abstract. Preclinical articles and/or articles that were clearly outside of the scope of the current review were removed prior to Stage 2 of screening. A low threshold was set to proceed to Stage 2 (ie, articles proceeded to Stage 2 if there was any chance at all of inclusion), to maximize sensitivity of the search while disregarding specificity at the current stage. In Stage 2, full texts of articles identified in Stage 1 were thoroughly reviewed for inclusion based on the following inclusion criteria. All published adult (age 18–75 years) human studies, written in English, assessing the effects of utilizing pharmacogenomic testing on improving clinical outcomes of MDD were included (ie, studies that assessed the efficacy of pharmacogenomic guided treatment). Of note, due to the known limited number of studies, there were no restrictions placed on quality of study, randomization, or use of a control group. As such, studies that were open-label, nonrandomized, nonblinded, or lacking a control group were also included. Bias and study quality were systematically assessed in each nonrandomized study using the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies (open source NOS tool available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), with greater number of stars indicative of higher study quality. All human studies seeking to evaluate the cost-effectiveness or potential cost savings of pharmacogenomic testing were also included as part of the second objective of the current review. Both retrospective and prospective studies were included in assessing the published literature on cost-effectiveness of pharmacogenetic testing for MDD.

Figure 1. PRISMA Flow Diagram



RESULTS

Search Results

After removal of duplicates, the initial search yielded 66 records (Figure 1). After Stage 1 of screening (ie, reviewing titles and abstracts), 13 full-text articles were evaluated for inclusion. Evaluation of full-text articles yielded 5 studies[25–29] assessing the effect of pharmacogenomic testing on MDD outcomes as summarized in Table 1. Systematic evaluation of study quality of nonrandomized trials was assessed using the NOS and is also summarized in Table 1. Five studies[30–34] were identified that assessed the cost-effectiveness or potential cost savings of pharmacogenomic testing for antidepressant selection as summarized in Table 2.

Pharmacogenomic Testing and MDD Outcomes

In subjects with MDD, only 5 studies have assessed for changes in clinical outcomes (ie, changes in depression severity, response or remission rates) as a result of prescribing guided by pharmacogenomic testing.[25–29] Three studies utilized GeneSight testing (developed and sold by AssureRx Health, Inc), a commercially available, combinatorial (ie, tests for multiple genes) pharmacogenomic test that analyzes tissue from a cheek swab and provides a report to aid prescribing choices based on the pharmacokinetic and pharmacodynamics profile of an individual. One study utilized the Genecept Assay (Genomind, King of Prussia, Pennsylvania), a combinatorial pharmacogenomics test that similarly guides prescribers based on predicted pharmacodynamics and pharmacokinetics.[28] Another study utilized CNSDose testing, a combinatorial pharmacogenomic test that solely assesses genes implicated in pharmacokinetics to aid in medication dosing.[29] Notably, at the current time, combinatorial pharmacogenomics has been shown to have significantly greater predictive value for antidepressant response compared to single gene tests[35]; however, in the future, it is possible that a single gene test may be discovered that may outperform combinatorial pharmacogenomics. The GeneSight report categorizes medications into advisory categories (bins) of "use as directed" (referred to as "green bin"), "use with caution" (referred to as "yellow bin"), and "use with caution and with more frequent monitoring" (referred to as "red bin") as well as noting which medications are unlikely to have a therapeutic effect.[25–27]

In the included studies, GeneSight tests for allelic variation of 6 genes: (1) CYP450 2D6 gene (*CYP2D6*), (2) CYP450 2C19 gene (*CYP2C19*), (3) CYP450 1A2 gene (*CYP1A2*), (4) serotonin transporter gene (*SLC6A4*), (5) CYP450 2C9 gene (*CYP2C9*), and (6) serotonin 2A receptor gene (*HTR2A*). The pharmacokinetic profile is determined by allelic variation in 4 CYP450 genes coding for the enzymes chiefly responsible for metabolism of the most frequently prescribed antidepressant medications (*CYP2D6, CYP2C19, CYP1A2,* and *CYP2C9*), while the pharmacodynamics profile is determined by allelic variation in serotonin receptor (*HTR2A*) and transporter (*SLC6A4*) genes involved in antidepressant response and tolerability.[25] Of note, the GeneSight gene panel has recently been updated and now includes *CYP3A4, CYP2B6, UGT1A4, UGT2B15, HLA-A,* and *HLA-B* genetic variants; however, these genes were not tested in the included studies.

In a prospective pilot study, Hall-Flavin et al[25] were the first to assess the potential change in clinical outcomes when utilizing GeneSight testing in MDD adult subjects. The clinical trial was funded partly by the Mayo Clinic Discovery Translation Grant, while genetic testing was fully funded by AssureRx Health, Inc. Of note, the Mayo Clinic is a founder and a stockholder in AssureRx Health, Inc. This nonrandomized, open-label, prospective cohort study utilized results from GeneSight testing to implement a pharmacogenomic algorithm designed to improve the safety and efficacy of prescribing antidepressant and antipsychotic medication. This study was in an outpatient psychiatric clinic that provided integrated treatments, with a substantial emphasis on psychotherapy, with psychiatrists who were not knowledgeable about genetic testing prior to entering the study. The study had 2 groups of subjects that were currently depressed, as defined by Hamilton Depression Rating Scale (HDRS-17) score ≥ 14: (1) the "unguided group" (n = 22), who received genetic testing but whose psychiatrists did not receive the results until after completion of the trial, and (2) the "guided group" (n = 22), who received testing and whose

Table 1. Clinical Trials Evaluating Outcomes in MDD When Utilizing Genetic Testing for Antidepressant Response

Study	Study Design	Study Subjects	Primary Results	Source of Funding/ Relevant Conflicts of Interest	Newcastle-Ottawa Scale[a]	Main Study Limitations
Hall-Flavin et al 2012[25]	8-week nonrandomized, open-label, prospective cohort study assessing clinical utility of GeneSight in an outpatient setting	Adult (18–75 y) subjects with *DSM-IV* diagnosis of MDD with HDRS-17 score > 14 were nonrandomly allocated into GeneSight-guided group (given GeneSight report at the beginning of 8-week trial) (n = 22) vs an unguided group (n = 22)	At primary endpoint (8 weeks), 18.2% reduction in HDRS-17 ratings for subjects in the unguided group compared with a 30.8% reduction for subjects in the guided group ($P = .04$)	AssureRx Health provided in-kind services consisting of genotyping, the GeneSight report, and shipping of buccal samples. Research was otherwise fully funded by a Mayo Clinic Discovery Translation Grant and the Samuel C. Johnson Genomics of Addiction Program	Selection: *** Comparability: 0 Outcome: *	Open-label, nonrandomized study design Partially industry funded
Hall-Flavin et al 2013[26]	8-week nonrandomized, open-label, prospective cohort study assessing clinical utility of GeneSight in an outpatient setting	Adult (18–72 y) subjects with *DSM-IV* diagnosis of MDD with HDRS-17 score > 14 were nonrandomly allocated into GeneSight-guided group (n = 114) vs an unguided group (n = 113)	At primary endpoint (8 weeks), 46.9% reduction in HDRS-17 scores in the guided group as compared to 29.9% reduction among the unguided group ($z = 3.14$, $P < .0001$). Significantly greater remission rates favored the guided group at a 26.4% remission rate vs the unguided participants at 12.9% (OR = 2.42; 95% CI, 1.09–5.39; $P = .03$)	Study authors Drs Winner and Allen were employed by the Mayo Clinic during the study; however, both are currently employed by AssureRx Health Inc, as is Dr Carhart. Dr Mrazek has developed intellectual property that has been licensed by AssureRx and incorporated into physician decision support software. He has received research funding from AssureRx to create and maintain a bibliographic system designed to regularly monitor the scientific literature. AssureRx provided in-kind services consisting of shipping of buccal samples, genotyping all patients' DNA, and providing the GeneSight report. Otherwise, research was funded by the Mayo Clinic Discovery Translation Grant	Selection: *** Comparability: 0 Outcome: *	Open-label, nonrandomized study design Partially industry funded
Winner et al 2013[27]	10-week randomized, double-blind (subjects and depression raters), prospective cohort study, assessing clinical utility of GeneSight in an outpatient setting	Adult subjects with *DSM-IV* diagnosis of MDD with HDRS-17 score > 14 were randomized to a GeneSight-guided group (n = 26) vs an unguided group (n = 25)	At primary endpoint (10 weeks), the guided group had 30.8% improvement in HDRS-17 scores as compared to 20.7% improvement in the unguided group ($P = .28$). Response and remission rates trended to favor the guided group; however, this also did not reach statistical significance for either response (OR = 2.14; 95% CI, 0.59–7.69) or remission (OR = 2.75; 95% CI, 0.48–15.80)	Study fully funded by AssureRx, and all authors are currently employed by AssureRx	NA (Newcastle-Ottawa Scale only applicable for nonrandomized clinical trials)	Fully industry funded Only trend was identified without statistically significant difference Study may have been underpowered
Brennan et al 2015[28]	3-month naturalistic, unblinded, prospective study assessing clinical utility of Genecept Assay in an outpatient setting	Adult subjects (> 18 y); clinicians were instructed to enroll patients with a primary diagnosis of depression and/or anxiety, although patients with other diagnoses were not excluded (n = 685)	At the end of the 3-month trial, 77% of participants showed improvement, with 39% showing a treatment response and 38% achieving full remission as per QIDS-SR scores, regardless of number of previous antidepressant trials	Study fully funded by Genomind, which also played a role in study design; the collection, management, and analysis of data; and the preparation, review, and approval of the manuscript	NA given lack of control group	Fully industry funded Unblinded In the absence of a treatment-as-usual comparator group, the proportion of improvement attributable to the test cannot be estimated

(continued)

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Table 1 (continued). Clinical Trials Evaluating Outcomes in MDD When Utilizing Genetic Testing for Antidepressant Response

Study	Study Design	Study Subjects	Primary Results	Source of Funding/ Relevant Conflicts of Interest	Newcastle-Ottawa Scale[a]	Main Study Limitations
Singh 2015[29]	12-week prospective double-blind (subjects and depression raters), randomized, cohort study assessing the clinical utility of proprietary pharmacokinetic interpretive report (CNSDose)	Caucasian adults with *DSM-5* diagnosis of MDD HDRS-17 score > 18 were randomized to a CNSDose-guided group (report guided medication dosing) (n = 74) vs unguided group (n = 74)	At the primary endpoint (12 weeks), subjects receiving genetically guided prescribing had a 72% remission rate, while the unguided group had a remission rate of 28% (OR = 2.52; 95% CI, 1.71–3.73, $P < .0001$) with an NNG = 3 (95% CI, 1.7–3.5) to produce an additional remission	The study was conducted and fully funded by Baycrest Biotechnology Pty Ltd, the developers of CNSDose	NA (Newcastle-Ottawa Scale applicable only for nonrandomized clinical trials)	Fully industry funded Report guided dosing only, not antidepressant selection

[a]Newcastle-Ottawa Scale uses a "star system" in which a greater number of stars is indicative of higher study quality; asterisks in table represent star ratings.
Abbreviations: CI = confidence interval, *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, NA = not applicable, NNG = number needed to genotype, OR = odds ratio, QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report.

psychiatrists were provided with the results at the beginning of the trial. The participants were informed of what group they were in (ie, guided or unguided). Other than receiving the results of the testing, there were no other differences in treatment (eg, psychotherapy) between groups. At the end of the 8-week trial, there was an 18.2% reduction in HDRS-17 ratings for subjects in the unguided group compared with a 30.8% reduction for subjects in the guided group ($P = .04$). Similarly, there was an average 7.2% reduction in the Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C_{16}) score for subjects in the unguided group compared with a 31.2% reduction in overall scores for subjects in the guided group ($P = .002$). The foregoing study provides preliminary evidence that pharmacogenomic testing could provide improved clinical outcomes; however, it had several limitations as the sample size was small, the study was not randomized, and there was no blinding. Additionally, the lack of blinding and randomization in combination with the presence of industry funding (ie, for genetic testing, report generation, and shipping) provides an additional source of potential bias.

Hall-Flavin et al[26] conducted a larger follow-up study in an attempt to replicate their previous findings. The study design was identical (ie, nonrandomized, open-label, prospective cohort study, mixed funding from industry and academia) except for the setting and the sample size. The current study setting was an outpatient psychiatric clinic that primarily provides psychopharmacologic treatment delivered by psychiatrists, whereas the clinic in the previous study primarily focused on psychotherapy. This study had a larger sample size, with 93 subjects in the unguided group and 72 subjects in the guided group completing the trial. At the end of the 8-week trial, there was a 46.9% reduction in HDRS-17 scores in the guided group as compared to a 29.9% reduction among the unguided group ($z = 3.14$, $P < .0001$). Similarly significant results favoring the guided group were found when change in QIDS-C_{16} ($z = 3.24$, $P < .0001$) and Patient Health Questionnaire-9 scores ($z = 3.26$, $P < .0001$) was analyzed. Significantly greater response rates (as indicated by > 50% reduction of depression severity scores) were found in the guided group versus the unguided group at week 8, as 44.4% of participants in the guided group responded, compared with 23.7% of participants in the unguided group (odds ratio [OR] = 2.58; 95% confidence interval [CI], 1.33–5.03; $P = .005$). Remission rates similarly favored the guided group, with guided participants achieving a higher rate of remission (26.4%) than unguided participants (12.9%) (OR = 2.42; 95% CI 1.09–5.39; $P = .03$). Therefore, this study provided further support for the ability of pharmacogenomic testing to improve clinical outcomes; however, it had the same limitations of the previously study, namely, lacking the necessary randomization and blinding. Additionally, 3 of the study authors (Winner, Allen, and Carhart) were employed by AssureRx Health, Inc at the time of publication.

Additionally, Winner et al[27] conducted a prospective, randomized, double-blind study assessing the clinical impact of GeneSight testing for MDD. The study was fully industry-funded, and AssureRx Health, Inc, employed all study authors. Depressed adult outpatients were randomized to an unguided treatment as usual (TAU) arm (n = 25) or a guided, pharmacogenomic-informed GeneSight arm (n = 26). Subjects were blinded to their treatment group, and blinded study raters assessed depression severity, whereas clinicians were not blinded, as this would not be possible. Within 2 days of enrollment, clinicians providing care for subjects in the guided group received the GeneSight report to help guide their prescribing. Antidepressant medication changes began within 2 weeks after baseline assessments. At the end of the 10-week trial, the

Table 2. Studies Evaluating Cost-Effectiveness and Cost Savings of Genetic Testing for Antidepressant Response in MDD

Study	Study Methodology	Results
Hornberger et al 2015[30]	Used Perlis et al[34] model to analyze cost-effectiveness of GeneSight testing by pooling the results from 3 studies assessing the clinical validity of GeneSight testing[25–27]	Combining the results of these 3 studies, estimated an increase in QALYs by 0.316 years and projected savings of $3,711 in direct medical costs and $2,553 in work productivity costs per patient over the lifetime Determined the probability of GeneSight testing being cost-effective at the willingness-to-pay threshold of $50,000 per QALY is 94.5% Authors concluded that combinatorial pharmacogenomics testing could be a cost-effective intervention; however, further investigation was needed
Winner et al 2015[31]	1-year, prospective study assessing pharmacy claims between a GeneSight-guided cohort and a propensity-matched control group. Included subjects with any Axis I diagnosis that augmented or switched to a different antidepressant or antipsychotic medication within the past 90 days Pharmacy claims were extracted from the Medco pharmacy claims database for each patient (n = 2,168) for 1 year following testing and compared to a 5-to-1 propensity-matched treatment as usual (TAU), standard of care control group (n = 10,880)	Subjects in the GeneSight-guided group saved on average $714.24 for nonpsychiatric medications and $321.36 for psychiatric medications, with $1,035.60 in total medication cost savings over the 1-year period compared to the nontested TAU cohort ($P = .007$)
Winner et al 2013[32]	1-year blinded and retrospective study evaluating 8 direct or indirect health care utilization measures for 96 patients with a *DSM-IV-TR* diagnosis of depressive or anxiety disorder The 8 measures were evaluated in relation to an interpretive pharmacogenomic test and reporting system (GeneSight)	Subjects whose medication regimen included a medication identified by the gene-based interpretive report as most problematic for that patient and are in the "red bin" (medication status of "use with caution and frequent monitoring") had 69% more total health care visits, 67% more general medical visits, greater than 3-fold more medical absence days, and greater than 4-fold more disability claims than subjects taking drugs categorized by the report as in the green bin ("use as directed") or yellow bin ("use with caution")
Olgiati et al 2012[33]	Used a simulated 12-week trial modeled on Sequenced Treatment Alternatives to Relieve Depression (STAR*D) data in which 5-HTTLPR genotyping was used to determine the likelihood of SSRI response and thus guided the selection of citalopram vs bupropion Applied model to conduct a cost-utility analysis in 3 European regions with high GDP (Euro A), middle GDP (Euro B), and middle-high GDP (Euro C)	From cost-effectiveness acceptability curves, the probability of genetic testing cost being below the WHO-recommended cost-utility threshold (3 GDP per capita = $1,926) was > 90% in high-income countries (Euro A), while in middle-income regions, these probabilities are < 30% (Euro B) and < 55% (Euro C), respectively If the cost of genetic testing decreased to $100 per test, this pharmacogenetic approach would likely become cost-effective in middle-income countries (Euro B)
Perlis et al 2009[34]	Retrospectively analyzed clinical and genetic data from the STAR*D study to assess cost-effectiveness of pharmacogenetic testing for antidepressant response, based on single-nucleotide polymorphism in the *HTR2A* gene	For a 40-year-old with MDD, the SSRI as first- and second-line strategy was both cheaper and more effective than all other no-test conditions. This finding was driven by the lower cost and lower treatment discontinuation rate associated with SSRI treatment compared to bupropion treatment. Compared to this strategy of treating all patients with an SSRI as first- and second-line therapy, the strategy of testing patients first and initiating those testing negative on bupropion cost an additional US $505.50 per patient but provided an additional 0.0054 QALY, yielding a cost of $93,520 per additional QALY

Abbreviations: GDP = gross domestic product, MDD = major depressive disorder, QALY = quality-adjusted life-year, SSRI = selective serotonin reuptake inhibitor, WHO = World Health Organization.

guided group had 30.8% improvement in HDRS-17 scores as compared to 20.7% improvement in the unguided TAU group; however, this difference did not reach statistical significance ($P = .28$). Similarly, response and remission rates trended to favor the guided group; however, they also did not reach statistical significance for either response (OR = 2.14; 95% CI, 0.59–7.69) or remission (OR = 2.75; 95% CI, 0.48–15.80).

Two studies were identified that did not utilize GeneSight testing. Brennan et al[28] utilized the commercially available Genecept Assay (Genomind, King of Prussia, Pennsylvania) that guides prescribing by assessing allelic variation in the following genes: *CYP2D6, CYP2C19, CYP3A4, SLC6A4, 5HT2C,* dopamine-2 receptor (*DRD2*), L-type voltage-gated calcium channel (*CACNA1C*), ankyrin g (*ANK3*), catechol-*O*-methyltransferase (*COMT*), and methylenetetrahydrofolate reductase (*MTHFR*). The study was fully funded by Genomind, which also played a role in study design; the collection, management, and analysis of data; and the preparation, review, and approval of the manuscript. This naturalistic study differed from the other 5 studies in that there was no control group; however, it was by far the largest study, with 685 participants. In this naturalistic, nonblinded, prospective study, all participants received genetic testing, and the results were utilized by all clinicians to guide prescribing based on the identified pharmacodynamics/pharmacokinetic profile, with 93% of clinicians reporting that the test results influenced their prescribing. Over the duration of the 3-month trial, 77% of participants showed improvement, with 39% showing a treatment response and 38% achieving full remission as per QIDS-Self Report scores, regardless of number of previous antidepressant

trials. Therefore, the authors concluded that a substantial proportion of individuals receiving pharmacogenomic testing showed clinically significant improvements; however, in the absence of a TAU comparator group, the proportion of improvement attributable to the test cannot be estimated.

The final identified study investigated the clinically utility of a proprietary pharmacokinetic interpretive report (CNSDose) that assesses CYP2D6, CYP2C19, and ABCC1 and ABCB1 transporters (ie, key blood-brain barrier drug transporters) polymorphisms to aid in medication dosing.[29] The study was conducted and fully funded by Baycrest Biotechnology Pty Ltd, the developers of CNSDose. This study was a 12-week prospective double-blind (ie, subjects and depression raters blinded), randomized, genetically guided versus unguided trial of antidepressant dosing in Caucasian adults (N = 148) with moderate to severe MDD as indicated by an HDRS-17 score ≥ 18. All subjects had genetic testing, but via computerized randomization, only half (ie, the guided group) had this information analyzed and a report sent to their prescriber to aid in antidepressant dosing. At the end of the 12-week trial, subjects receiving genetically guided prescribing (n = 74) had a 72% remission rate, while the unguided group (n = 74) had a remission rate of 28%. These results suggested a 2.52-fold greater chance of remission (95% CI, 1.71–3.73; $P < .0001$) with a number needed to genotype (NNG) = 3 (95% CI, 1.7–3.5) to produce an additional remission. The details of how the generated report guided prescribing were not explicitly described, and as such it was unclear how the author was able to achieve such high remission rates (ie, rates significantly higher than remission rates described in STAR*D or any other clinical drug trial) in the tested group. The author concluded that the results suggested improved efficacy secondary to guidance from genetic testing but that the results must be independently replicated prior to being translated into clinical care, given that this was the first and only study assessing the utility of the CNSDose system.[29]

Potential Cost Savings and Cost-Effectiveness of Pharmacogenomic Testing for MDD

In theory, pharmacogenomic testing may increase cost-effectiveness through improving the rate (ie, by decreasing lag time for clinical improvement) or amount (ie, by increasing response and remission rates) of therapeutic improvement and thereby decreasing the direct and/or indirect costs of MDD. As with any test or intervention, the cost of the test must be weighed against the resultant cost savings to determine its cost-effectiveness. Although there is no accepted threshold below which interventions should be funded, one widely cited number, based on the cost-effectiveness of dialysis in chronic renal failure patients covered by Medicare, is a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-years (QALYs),[36] and few interventions with cost-effectiveness ratios exceeding $100,000 per QALY receive funding.[37] These cost metrics must also be considered when evaluating the cost-effectiveness of pharmacogenomic testing for MDD.

Five articles were identified assessing the cost-effectiveness and potential cost savings of pharmacogenomic testing for MDD (Table 2). Perlis et al retrospectively analyzed clinical and genetic data from the STAR*D study to assess cost-effectiveness of pharmacogenetic testing for antidepressant response.[34] In this study, the authors focused on a single-nucleotide polymorphism in the *HTR2A* gene, which was associated with citalopram response.[38] The result of this test was then applied to determine if an individual should have been trialed first on bupropion instead of citalopram and the cost-effectiveness of this strategy.

For a 40-year-old person with MDD, the selective serotonin reuptake inhibitor (SSRI) as first- and second-line strategy was both cheaper and more effective than all other no-test conditions. This finding was driven by the lower cost and lower treatment discontinuation rate associated with SSRI treatment compared to bupropion treatment. Compared to this strategy of treating all patients with an SSRI as first- and second-line therapy, the strategy of testing patients first and initiating those testing negative on bupropion cost an additional $505.50 (US dollars) per patient but provided an additional 0.0054 QALY, yielding a cost of $93,520 per QALY. Relative to the aforementioned WTP threshold of $50,000, the genetic test as found by Perlis et al would not be considered cost-effective or advisable for public funding. Of note, as the cost association with genetic testing decreases, the model would require adaptation. The authors noted, in the extreme example if testing was free, the cost per QALY is less than $1,000 using their model.[34]

Olgiati et al[33] applied a similar model to evaluate the cost utility of incorporating serotonin transporter (5-HTTLPR) genotyping in the treatment of MDD. As with the previous study, Olgiati et al used a simulated 12-week trial modeled on STAR*D data in which 5-HTTLPR genotyping was used to determine the likelihood of SSRI response and thus guided the selection of citalopram versus bupropion. The authors applied their model to conduct a cost-utility analysis in 3 European regions with high gross domestic product (GDP) (Euro A), middle GDP (Euro B), and middle-high GDP (Euro C). From cost-effectiveness acceptability curves (CEAC), the probability of genetic testing cost being below the WHO recommended cost-utility threshold (3 GDP per capita = $1,926) was > 90% in high-income countries (Euro A), while in middle-income regions, these probabilities are < 30% (Euro B) and < 55% (Euro C), respectively. The authors noted that if the cost of genetic testing decreased to $100 per test, this pharmacogenetic approach would likely become cost-effective in middle-income countries (Euro B).[33]

More recent studies have analyzed the potential cost savings and cost-effectiveness of GeneSight testing specifically. Winner et al retrospectively analyzed the increase in direct and indirect health resource utilization for subjects that received antidepressants that could have been predicted to be inappropriate based on GeneSight testing.[32] Subjects whose medication regimen included a medication identified by the GeneSight interpretive report as most

problematic (ie, in the "red bin" indicative of medications to be "used with caution and frequent monitoring") had 69% more total health care visits, 67% more general medical visits, greater than 3-fold more medical absence days, and greater than 4-fold more disability claims than subjects taking drugs categorized by the report as in the "green bin" ("use as directed") or "yellow bin" ("use with caution"). Additionally, the mean health care utilization cost calculated for subjects taking red bin medications was $5,188 (US dollars) greater, compared with subjects using green bin or yellow bin medications. Of note, the current study did not calculate metrics of cost-effectiveness, but rather focused on increased costs for subjects taking red bin medications. Further, of the 97 subjects, only 9 (9%) of the subjects were taking red bin medications. Therefore, while GeneSight testing might have saved costs and/or improved outcomes for 9% of the subjects, costs would have increased for the other 91% and most likely not have affected management or outcomes for these subjects. As such, while the current study suggests potential cost savings for some, they did not demonstrate cost-effectiveness for the group as a whole.

Winner et al[31] also assessed cost savings of GeneSight testing specifically focusing on overall pharmacy costs in a 1-year prospective evaluation of subjects who had switched or added a new psychiatric medication after having failed monotherapy for their psychiatric disorder within the past 90 days. Notably, the sample was not restricted to MDD and included subjects with anxiety disorders (19.7%), depressive disorders (28.3%), bipolar disorder (5.7%), and psychotic disorders (< 1%). Pharmacy costs for subjects receiving GeneSight guided care (n = 2,168) were compared to a TAU unguided group that did not receive testing (n = 10,880) over a 1-year period. Subjects in the GeneSight guided group saved on average of $714.24 for nonpsychiatric medications and $321.36 for psychiatric medications with $1,035.60 in total medication cost savings over the 1-year period compared to the nontested TAU cohort ($P = .007$). Similar to the previous study, this study did not evaluate the cost-effectiveness of genetic testing, as the primary outcome was pharmacy cost savings and did not integrate other factors (ie, cost of the genetic testing, etc) to estimate the cost per QALY when using the test.

More recently, Hornberger et al analyzed the results from the previously discussed clinical validity studies[25–27] to determine the cost-effectiveness of GeneSight testing.[30] Combining the results of these 3 studies, Hornberger et al estimated an increase in QALYs by 0.316 years and projected savings of $3,711 in direct medical costs and $2,553 in work productivity costs per patient over the lifetime. Further, based on their analysis, the probability of GeneSight testing being cost-effective at the WTP threshold of $50,000 is 94.5%. Therefore, their results suggested that combinatorial pharmacogenomic testing could be a cost-effective intervention. Notably, however, their projections were based mostly on studies of poor quality, lacking appropriate randomization and blinding; to determine efficacy of GeneSight testing, 93.3% of the pooled results was based on 2 open-label, nonrandomized studies,[25,26] while only 6.7% of their pooled results was based on a randomized, controlled, and double-blinded study.[27] Therefore, the pooled efficacy (pooled effect of testing on response rate calculated to be 1.71 [95% CI 1.17–2.49]) was based mostly on low-quality studies. Since the model of cost-effectiveness is heavily weighted on intervention efficacy effect size, the validity of the results of this analysis is questionable as the reliability of the calculated efficacy may be poor.

DISCUSSION

The current review identified a limited number of studies that have evaluated the impact of pharmacogenomic testing on clinical outcomes in MDD subjects. Two open-label, nonrandomized, prospective cohort studies suggested a positive effect of GeneSight pharmacogenomic testing on clinical outcomes; however, the lack of randomization and blinding was a significant methodological limitation identified in both of these studies.[25,26] Further, the only randomized, controlled, and double-blinded clinical trial using GeneSight did not find a statistically significant difference in response or remission rates when comparing subjects with pharmacogenomic testing versus subjects without testing.[27] One randomized, controlled, double-blinded clinical trial using CNSDose found significantly increased remission rates at the end of a 12-week trial when using the pharmacokinetic interpretive report to guide antidepressant dosing.[29] However, these promising results have yet to be independently replicated.

In all of the included studies, significant bias was identified. The majority of studies were not randomized or blinded. All studies had industry funding and frequently had authors with significant conflicts of interest. Further, regulations for external monitoring of studies assessing genetic testing are absent as compared to the ample external monitoring of clinical drug trials. In clinical drug trials, regulatory agencies may directly reanalyze raw data and visit study sites. At the current time, no such regulations exist for studies assessing the utility of pharmacogenomic testing. As such, this lack of regulation introduces another source of potential bias.

Studies assessing the cost-effectiveness and potential cost savings of pharmacogenomic testing were similarly limited. One study evaluated the cost-effectiveness of testing using data from the STAR*D study to retrospectively model and determine the cost per QALY of *HTR2A* gene testing for antidepressant response prediction.[34] The estimated cost per QALY was $93,520, well above the usual WTP threshold of $50,000. Of note, however, this study was conducted in 2009 when genetic testing was more costly and only assessed a single gene (*HTR2A*), which has been shown to have less predictive value compared to combinatorial pharmacogenomics methods.[35] Olgiati et al similarly assessed the cost-effectiveness of 5-HTTLPR testing in 3 European regions, finding that pharmacogenetic testing was likely only to be cost-effective in high-income countries.[33]

While these 2 studies assessed the cost-effectiveness of single gene testing, the efficacy studies discussed all used combinatorial pharmacogenomic testing, assessing multiple genes to evaluate pharmacodynamics and pharmacokinetics of psychiatric medications. Two studies suggested some areas of cost savings for combinatorial pharmacogenomic testing for a subset of individuals, namely those who have been prescribed red bin medications that are to be used with caution.[31,32] One study conducted a more in-depth pharmacoeconomic analysis of GeneSight testing, suggesting that it was cost-effective and likely to be well below the WTP threshold of $50,000; however, their model estimated efficacy primarily based on nonrandomized, nonblinded studies, and therefore their results might not be valid.[30] Therefore, future cost-effectiveness studies are required to confirm their findings based on efficacy effect sizes determined by high-quality studies.

The main limitation of the current systematic review was the limited number of studies identified. While this is an important limitation of the current analysis, it is also a significant finding. The lack of evidence for pharmacogenomic testing for MDD has important implications, especially considering the increased use of these costly tests in clinical practice without an adequate evidence base to support their use. Also of note, the impact on MDD outcomes with the clinical use of these tests may vary greatly from outcomes found in controlled study settings, as recent evidence suggests that fewer than half of clinicians refer to the results of pharmacogenomic tests when ordered.[39]

Another limitation of the current review was the inability to assess at what point in the treatment of MDD pharmacogenomic testing should be utilized. The included studies did not assess the relative utility of testing prior to selection of the first antidepressant to be trialed versus testing after a pattern of treatment resistance or intolerance has been established. Determining the appropriate time for testing would also be important from a cost-effectiveness standpoint to determine at what point evidence-based funding should be provided for testing during the treatment of MDD. While the current studies did not assess this question, results from the STAR*D trial would suggest that earlier testing (ie, with the selection of the first or second antidepressant trial) may have the greatest utility given that once a patient has received several adequate trials of existing monoaminergic antidepressants, the likelihood of responding to a monoaminergic antidepressant drops precipitously, suggestive of treatment resistance to monoaminergic agents in general rather than the specific antidepressants trialed. For these patients, novel antidepressants, combinations, augmenters, and/or nonpharmacologic treatments may be more appropriate, and as such currently available genetic testing may be less applicable to this patient population.

In conclusion, currently available evidence for improved clinical outcomes from pharmacogenomic testing is limited. Clinical trials suggestive of a positive effect of pharmacogenomic testing on clinical outcomes in MDD were mostly of low quality, often lacking randomization and blinding, and were vulnerable to bias from industry funding. Further, results from a randomized, double-blind clinical trial of GeneSight did not reach statistical significance; however, notably, they may have been underpowered. One randomized, double-blind clinical trial of CNSDose found a statistically significant increase in remission rates, but this has yet to be independently replicated.[29] Taken together, results from these studies suggest that further studies are required and merited to determine the impact of these tests on clinical outcomes, namely in the rate (ie, time to improvement) and amount (ie, response and remission rates) of therapeutic improvement. Well-designed clinical trials with adequate sample sizes, randomization, and blinding are required prior to the routine implementation of pharmacogenomic testing into clinical practice. If testing is found to improve clinical outcomes, the cost-effectiveness of testing should also be further evaluated based on the results from high-quality studies.

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