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Systematic Review

Impact of Pharmacogenomics Testing on Response to Antidepressants and Antipsychotics - A Systematic Review

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Abstract:

Introduction: With the sequencing of the human genome and the subsequent revelation of the genetic structures underlying many complex illnesses and responses to many treatments, precision medicine has emerged as a new player in the healthcare setting. We aimed to assess the Impact of pharmacogenomics testing on response to Antidepressants and Antipsychotics.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review. This systematic review identified PubMed, PMC, and Medical Literature Analysis and Retrieval System Online (MEDLINE), Supplementation of the available articles for the review was done using Google Scholar and Research Gate.

Results: Ten study articles were included after analyzing 12408 papers. These studies were gathered by searching through Mesh advanced search strategy and regular keywords with Boolean search strategy through multiple databases. The next step was screening the titles, and abstracts and only 166 papers passed through the full-text screening according to the inclusion and exclusion criteria. The quality of the included 166 studies was assessed using the Cochrane risk of bias tool for randomized trials. Finally, ten studies resulted from the qualitative synthesis and were included in this systematic review.

Conclusion: combinatorial pharmacogenomics testing has the potential to be a useful tool in directing the treatment of depression in different age cohorts. In addition, it has a role in response improvement among patients with previous antidepressant failure.

Keywords: Precision medicine, personalized medicine, pharmacogenomics testing, individualized medicine, predictive medicine and Antidepressant Drug.

Introduction and Background:

At some point in life, approximately one out of every five Americans might fulfill the diagnostic criteria for either an anxiety disorder or a depressive disorder; antidepressants are frequently used to treat these conditions [1]. Approximately 13% of the general population takes antidepressant medications [2]. The most prevalent mental illness in the world, major depressive disorder, also referred to as MDD is a major contributor to years spent disabled, which has a significant socioeconomic impact [3]. Precision medicine has become a new player in healthcare along with the sequencing of the human genome and the subsequent identification of the genetic structures underlying many complicated disorders [4, 5]. Despite a steady rise in recognition among doctors, consumers, and stakeholders from both the public and private sectors over the past decade, there is still a lack of adequate understanding regarding its precise definition, characteristics, and the intricate operational strategies that go along with putting it into practice. Precision medicine, for example, is widely acknowledged to be transforming the clinical care paradigm from the old evidence-based approach (based on data collected in large groups of patients) to an individual-based deep knowledge of biological and clinical (phenotypic) characteristics [6]. The major objectives of MDD treatment are long-term therapeutic effect maintenance and remission. The effectiveness of pharmacological treatment remains inadequate even with the availability of various classes of antidepressant medications. As a result, matching a patient to the best course of treatment typically necessitates multiple trials of various treatments, with the alarming conclusion that the more unsuccessful treatments tried, the less likely a successful outcome is. After the initial course of treatment, only about one-third of patients get remission, and around a third experienced treatment-resistant depression (TRD) [7, 8]. At the moment, prognosis is predicted by professionals using established risk factors. Just as oncologists already utilize biomarkers to predict disease prognosis and guide treatment options, researchers may soon be able to find genetic biomarkers that indicate worse outcomes or more severe phenotypes owing to developments in genomics. To ascertain the influence of pharmacogenomics testing on clinical outcomes in MDD, the current systematic review looks at the body of existing evidence.

Methods:

A systematic literature review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9]. A search was performed in the PubMed, PMC, Medical Literature Analysis and Retrieval System Online (MEDLINE), and

Google Scholar databases. Additional articles were retrieved from Research Gate by inspecting the reference list of reviewed articles and searching by keywords. The search for articles was done by Mesh advanced search strategy for PubMed, PMC, and MEDLINE. Regular Keywords with Boolean for Google Scholar and Research Gate [Table 1]. The articles were chosen based on their quality and relevancy. We used the Cochrane risk of bias tool for randomized trials to assess the quality and risk of bias in randomized clinical trials that included screening their title, abstract, and full text [Table 2] [10]. All articles and abstracts screening was performed based on inclusion and exclusion criteria. Parallel, randomized, controlled trials of young adults, adults, or old age populations, that compare the pharmacogenomics guided therapy to treatment as usual (TAU) in psychiatry, and published between January 2019- December 2023 were included. Studies of animals, other than the English language, thesis, conference, abstracts, and studies before January 2019 were excluded.

[Table 1] Databases with Their Search Term Strategy:

Databases	Search strategy
PubMed, PMC and Medical Literature Analysis and Retrieval System Online (MEDLINE).	Mesh advanced search: ("precision medicine"[MeSH Terms] OR ("precision"[All Fields] AND "medicine"[All Fields]) OR "precision medicine"[All Fields] OR ("precision medicine"[MeSH Terms] OR ("precision"[All Fields] AND "medicine"[All Fields]) OR "precision medicine"[All Fields] OR ("personalized"[All Fields] AND "medicine"[All Fields]) OR "personalized medicine"[All Fields]) OR (("pharmacogenetics"[MeSH Terms] OR "pharmacogenetics"[All Fields] OR "pharmacogenomic"[All Fields] OR "pharmacogenomics"[All Fields] OR "pharmacogenomically"[All Fields]) AND ("test s"[All Fields] OR "tested"[All Fields] OR "testing"[All Fields] OR "testings"[All Fields] OR "tests"[All Fields])) OR ("precision medicine"[MeSH Terms] OR ("precision"[All Fields] AND "medicine"[All Fields]) OR "precision medicine"[All Fields] OR ("individualized"[All Fields] AND "medicine"[All Fields]) OR "individualized medicine"[All Fields]) OR ("precision medicine"[MeSH Terms] OR ("precision"[All Fields] AND "medicine"[All Fields]) OR "precision medicine"[All Fields] OR ("predictive"[All Fields] AND "medicine"[All Fields]) OR "predictive medicine"[All Fields]) OR ("precision medicine/classification"[MeSH Major Topic] OR "precision medicine/instrumentation"[MeSH Major Topic] OR "precision medicine/methods"[MeSH Major Topic] OR "precision medicine/standards"[MeSH Major Topic] OR "precision medicine/trends"[MeSH Major Topic])) AND ("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND (("antidepressive agents"[Pharmacological Action] OR "antidepressive agents"[MeSH Terms] OR ("antidepressive"[All Fields] AND "agents"[All Fields]) OR "antidepressive agents"[All Fields] OR ("antidepressant"[All Fields] AND "drug"[All Fields]) OR "antidepressant drug"[All Fields] OR ("antidepressent"[All Fields] OR "antidepression"[All Fields] OR "antidepressive agents"[Pharmacological Action] OR "antidepressive agents"[MeSH Terms] OR ("antidepressive"[All Fields] AND "agents"[All Fields]) OR "antidepressive agents"[All Fields] OR "antidepressant"[All Fields] OR "antidepressants"[All Fields] OR "antidepressive"[All Fields] OR "antidepressives"[All Fields]) OR ("antidepressive agents/administration and dosage"[MeSH Major Topic] OR "antidepressive agents/adverse effects"[MeSH Major Topic] OR "antidepressive agents/metabolism"[MeSH Major Topic] OR "antidepressive agents/pharmacokinetics"[MeSH Major Topic] OR "antidepressive agents/pharmacology"[MeSH Major Topic] OR "antidepressive agents/poisoning"[MeSH Major Topic] OR "antidepressive agents/therapeutic use"[MeSH Major Topic] OR "antidepressive agents/toxicity"[MeSH Major Topic]) OR ("antipsychotic agents"[Pharmacological Action] OR "antipsychotic agents"[MeSH Terms] OR ("antipsychotic"[All Fields] AND "agents"[All Fields]) OR "antipsychotic agents"[All Fields]) OR ("antipsychotic agents"[Pharmacological Action] OR "antipsychotic agents"[MeSH Terms] OR ("antipsychotic"[All Fields] AND "agents"[All Fields]) OR "antipsychotic agents"[All Fields] OR ("major"[All Fields] AND "tranquillizing"[All Fields] AND "agents"[All Fields])) OR ("antipsychotic agents"[Pharmacological Action] OR "antipsychotic agents"[MeSH Terms] OR ("antipsychotic"[All Fields] AND

	"agents"[All Fields]) OR "antipsychotic agents"[All Fields] OR ("antipsychotic"[All Fields] AND "drug"[All Fields]) OR "antipsychotic drug"[All Fields]) OR ("antipsychotic agents"[Pharmacological Action] OR "antipsychotic agents"[MeSH Terms] OR ("antipsychotic"[All Fields] AND "agents"[All Fields]) OR "antipsychotic agents"[All Fields] OR ("neuroleptic"[All Fields] AND "agent"[All Fields]) OR "neuroleptic agent"[All Fields]) OR ("antipsychotic agents/administration and dosage"[MeSH Major Topic] OR "antipsychotic agents/adverse effects"[MeSH Major Topic] OR "antipsychotic agents/metabolism"[MeSH Major Topic] OR "antipsychotic agents/pharmacokinetics"[MeSH Major Topic] OR "antipsychotic agents/pharmacology"[MeSH Major Topic] OR "antipsychotic agents/poisoning"[MeSH Major Topic] OR "antipsychotic agents/therapeutic use"[MeSH Major Topic] OR "antipsychotic agents/toxicity"[MeSH Major Topic])) AND ("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type])) AND (("Treatment Outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "Treatment Outcome"[All Fields] OR ("Treatment Outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "Treatment Outcome"[All Fields] OR ("patient"[All Fields] AND "relevant"[All Fields] AND "outcome"[All Fields]) OR "patient relevant outcome"[All Fields]) OR ("Treatment Outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "Treatment Outcome"[All Fields] OR ("clinical"[All Fields] AND "effectiveness"[All Fields]) OR "clinical effectiveness"[All Fields]) OR ("Treatment Outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "Treatment Outcome"[All Fields] OR ("treatment"[All Fields] AND "effectiveness"[All Fields]) OR "treatment effectiveness"[All Fields]) OR ("Treatment Outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "Treatment Outcome"[All Fields] OR ("treatment"[All Fields] AND "efficacy"[All Fields]) OR "treatment efficacy"[All Fields]) OR ("Treatment Outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "Treatment Outcome"[All Fields] OR ("treatment"[All Fields] AND "efficacy"[All Fields]) OR "clinical efficacy"[All Fields]) OR "Treatment Outcome"[MeSH Major Topic]) AND ("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type])).
Google scholar	Regular Keywords with Booleans : Precision medicine OR Personalized medicine OR pharmacogenomics testing OR Individualized Medicine OR Predictive medicine AND Antidepressant Drug OR Antidepressants OR antipsychotics AND Treatment outcome OR Patient-Relevant Outcome OR Clinical Effectiveness OR Treatment Effectiveness OR Treatment Efficacy OR Clinical Efficacy
Research Gate	Regular Keywords with Booleans : Precision medicine OR Personalized medicine OR pharmacogenomics testing OR Individualized Medicine OR Predictive medicine AND Antidepressant Drug OR Antidepressants OR antipsychotics AND Treatment outcome OR Patient-Relevant Outcome OR Clinical Effectiveness OR Treatment Effectiveness OR Treatment Efficacy OR Clinical Efficacy

[Table 2] The Quality Assessment of the Randomized Clinical Trials by Cochrane Risk of Bias Tool:

Study ID	*Random sequence*	*Allocation concealment (selection*	*Blinding of participants*	*Blinding of outcome*	*Incomplete outcome*	*Selective outcome*	*Other bias*	Over all
These 2019	low	low	low	low	Unclear	low	low	low
Tiwar 2022	low	low	low	low	Unclear	low	low	low

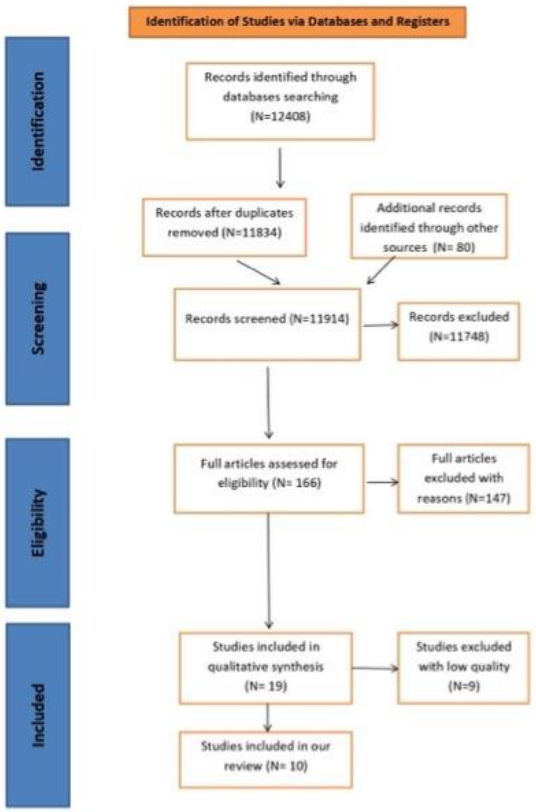
	Engelmann 2022	Papastergiou 2020	McCarthy2021	Vande Voort2022	Perlis 2020	Forester 2021	vanderschans2019	Greden2019
	low	low	low	low	low	low	low	low
	low	unclear	low	low	low	low	low	low
	low	low	low	unclear	low	low	low	low
	low	low	low	low	low	low	low	low
	unclear	low	low	low	low	unclear	low	low
	low	low	low	low	low	low	low	low
	low	low	low	low	low	low	low	low
	low	low	low	low	low	low	low	low

Results:

We identified 104 relevant articles through PubMed, PMC, and Medline by Mesh advanced search. Through Google Scholar we gathered 12200 articles by regular keywords with Boolean search. Research Gate was used to retrieve 80 relevant papers. Around 574 duplicates were removed. The remaining articles have been screened through their titles and abstracts, A Microsoft Excel spreadsheet file was generated to include all of the studies selected during the first screening step. According to the exclusion criteria all the systematic reviews, literature reviews, updates, and book chapters were excluded. We obtained 166 studies as full text. In total 19 studies met the inclusion criteria, (see Figure 1 for PRISMA diagram) [9]. All included studies were randomized controlled trials. The risk of bias in these studies varied: ten studies were rated "low risk", one "unclear", and eight "high risk", therefore only ten studies with low risk of bias according to the Cochrane risk of bias tool were included (see Table 2) [10]. Three studies assess the effectiveness of use combinatorial pharmacogenomics testing for informing medication selection in specific Age Groups. Six studies evaluate the role of pharmacogenomics guided treatment in difficult-to-treat depression cohort. One study establishes the linking of differential methylation to antidepressant treatment response. Overall, 3853 patients met eligibility criteria, 1288 males and 2565 females. All participants were randomized to treatment as usual (TAU) or guided care after pharmacogenomics testing; hence the included studies in this systematic review addressed the efficacy of precision medicine in the treatment of major depressive disorder and anxiety.

The body of research supporting the use of pharmacogenomics to enhance antidepressant precision is growing.

Figure 1: PRISMA Flow Diagram of the Inclusion and Exclusion Process of the Studies in the Systematic Review.



Discussion:

We thoroughly reviewed and evaluated the relevant studies about pharmacogenomics-guided treatment with a focus on its effectiveness and compared it to treatment as usual (TAU) in different aspects.

The Effectiveness of Use Combinatorial Pharmacogenomics Testing for Informing Medication Selection in Specific Age Groups:

Retained records related to that such as the randomized clinical trial conducted by Forester in 2021, which included 206 older adult patients (TAU, n=108; guided-care, n= 98), in both treatment arms the mean age was 68 years, the mean baseline Hamilton Depression Rating Scale (HAMD-17) was 19.8 (SD: 5.0) (severe depression) was equivalent roughly between study arms, with around one-third of patients falling into each of moderate, severe and very severe depression categories. Additionally, the cardiovascular comorbidities were the same between arms. At week eight, 184 patients completed the trial (TAU, n=98; guided-care, n=86). The response rate was significantly higher in the guided-care arm (29.6%) than in TAU (16.1%) (P= 0.032). The remission rate in guided care was (20.1%) significantly higher than TAU (7.4%) arm (P=0.014). In addition, this study observed a 26.7 % decrease in HAM-D17 score among the guided-care arm compared with an 18.7% decrease in the TAU arm, this difference in mean percent symptom improvement did not reach statistical significance (P=0.102). An additional insignificant difference between both arms was in the frequency of drug adverse effect events, about 10.2 % in TAU and 7% in guided care (P=0.435). This study was the first analysis evaluating the prospective clinical utility of combinatorial pharmacogenomics testing in the geriatric population. Despite its limitations which include small older patients' subset size, reduced ethnic diversity, and the short period to assess the outcome at eight weeks underestimate the benefits of pharmacogenomics-guided treatment in older patients [11].

In comparison with the study of Vanderschans which took place between Feb 2013 and Feb 2017. Totally 181 adults were considered for inclusion and only 106 finished the trial with a mean age of 70.7(6.9) with no significant differences in patients' characteristics except for differences in the presence of comorbidities (P=0.035). In this study elderly patients were randomly allocated to one of the study arms; deviating genotype intervention (DG-I), deviating genotype control (DG-C), and nonrandomized control arm. This study measured the primary outcome in terms of time needed to reach adequate drug levels in the blood within the therapeutic dose and no dose adjustments within the last Three weeks. The results showed no significant difference in the mean time to adequate dose between DG-I and DG-C arms. In contrast, there is a significantly faster rate in the DG-I arm compared with the nonrandomized control arm (0.004), but a non-significant difference was observed between the DG-C arm and the nonrandomized control arm (0.087). Therefore this clinical trial does not support accelerating dose adjustment for nortriptyline and venlafaxine in elderly patients with depression based on pharmacogenomics CYP2D6 screening. There are many factors affecting the results of this study. First, patients who finished the trial were significantly younger compared with patients who did not finish it, and in the vulnerable elderly population, the impact of genetic information may be particularly significant. Second, the effect of EM genotype patients is missing because they are considered as a control group. Finally, this trial did not meet the number of participants according to the sample size calculation [12].

Among the adolescent age group, Vande Voort performed a clinical trial, published in 2021. 176 adolescents with major depressive disorder, and a mean age of 15.5 (1.5), were randomized to the pharmacogenomics-guided treatment group (N= 84) and TAU group (N= 92).

Anxiety problems were a prevalent comorbidity that affected about 41% of the GENE and TAU cohort. The second most common comorbidity was Attention-deficit/hyperactivity disorder (ADHD) with about 17% in the GENE arm and 19% in the TAU arm. This study measured the mean CDRS-R scores for both arms at week eight and showed no statistical difference in the change from baseline (P=0.889) or six months (P= 0.558). In addition, there were no statistically significant differences between both arms, in the response and remission rates based on CDRS-R and QIDS at any time point. Regarding the number of side effects, no difference was observed between both arms at week eight (P=0.28), or six months (P=624). The study concluded that pharmacogenomics-guided treatment did not show outcome improvement in comparison to TAU in the adolescent age cohort. Multiple factors should be considered in this trial, such as the most of the sample was from the white population and there is a psychotherapy role that was not controlled during the study and any improvement may be linked to it (Table 3) [13].

Table 3: The Characteristics of Studies that Evaluate the Effectiveness of Use Combinatorial Pharmacogenomics Testing for Informing Medication Selection in Specific Age Groups

Author and year of publication	Intervention studied	Number of patients	Age Mean(SD)	Type of study	Result/ Conclusion
Forester et al, 2021 [11].	Combinatorial pharmacogenomics testing for informin	206	68(4.3)	RCT	When choosing a drug for older persons with depression

	g medication selection compare with Treatment as usual.				, combinatorial pharmacogenomics tests informed treatment selection led to better results than TAU.
Vanderschans et al, 2019 [12].	Specific genotype accompanied by a standardized dosing recommendation based on patients' genotype	106	70.7(6.9)	RCT	The results of study do not support pharmacogenomics CYP2D6 screening to accelerate dose adjustment for Nortriptyline and venlafaxine in older patients with depression.
Vande Voort et al, 2022 [13].	Treatment as usual (TAU) in comparison with pharmacogenomics guided treatment of MDD	176	15.5 (1.5)	RCT	Combinatorial pharmacogenomics guided treatment did not demonstrate improved outcome compared to TAU in adolescents with MDD.

The Role of Pharmacogenomics Guided Treatment in Difficult-to-Treat Depression Cohort:

In terms of the response and remission rates in previous failed MDD patients' therapy, several studies were reviewed, including a large, patient and rater-blinded, randomized, controlled study carried out by Greden and his team and published in 2019. At baseline, weeks eight, 12, 16, and 24. In Total, 1398 patients (TAU, n= 717; guide-care, n=681) were assessed by the 17-item Hamilton Depression ranging scale (HAM-D17) as a primary outcome. The secondary outcome was measured by a 16-item Quick Inventory of Depression symptomology (QIDS-C16) and a 9-item Patient Health Questionnaire (PHQ-9). The included patients' mean age was 47.5 years, with the majority female (70.6%), and they were diagnosed with MDD according to the assessment tools at screening and baseline time. In addition, they had unresponsiveness to at least one of the documented treatments. Patients with suicidal risk, significant medical conditions, or mild depression (less than 14 on HAM-D17) were excluded. The most common psychiatric comorbidity among the participants was General anxiety disorder. At week eight, symptom improvement showed no statistical difference between guided care and TAU (P=0.107); However, there is a statistically significant improvement in response and remission rates among guided care over TAU (P=0.013), (p=0.007) respectively. Another analysis conducted in this trial that supports the role of precise medicine compares patients who switched to congruent medication and those who remained on incongruent medication at week eight. There is significant statistical improvement in symptom, response, and remission rates that favors the congruent medication over the incongruent medication (P=0.002), (P=0.036), and (P=0.007) respectively. This study concludes that pharmacogenomics did significantly improve response and remission rates in treatment-resistant patients, particularly for patients who are treated with medications that are incongruent with their gene report. The factors that limited this study's strength are that the majority of participants are Caucasians, and the clinicians were not blinded which to mitigate this limitation; patients, central and site raters were blinded. Additionally, the exclusion of patients with mild depression limited the generalizability of its findings [14].

In contrast, compared to the previous study, Thase published in 2019 their clinical trial outcome of 912 participants. The results showed at eight weeks; the symptoms improved with significant statistical difference in the guided-care arm over the TAU (P=0.029). Additionally, it supports the last study results in terms of response rate and remission rate faster in the guided care arm than TAU, with statistically significant differences (P=0.008), (P=0.003) respectively. This study concludes that there is a significant improvement in patients with at least one year of failed MDD treatment. Although non-genetic factors may also lead to drug failure, their impact on patient outcomes cannot be examined because they were not collected in this guided trial [15].

Another 213 patients with major depressive disorder participated in a randomized controlled trial conducted in Canada and published in 2020. The trial assessed the difference between pharmacogenomics-guided and standard antidepressant treatment in a community pharmacy setting. The diagnoses of the participants included GAD (n = 165), MDD (n = 169), and other disorders (n = 10; e.g., eating disorders or anxiety

disorders). Most of the participants (n = 133) met the criteria for more than one current psychiatric diagnosis, with the majority showing both GAD and MDD (n = 124). Participant profiles were generated on the Pillcheck portal, and the pharmacists oversaw the buccal swab DNA collection procedure and assisted with Pillcheck registration. In Between study groups, there were no variations in the baseline PHQ-9 primary result, and there were also no differences in the two secondary outcomes (SDS and GAD-7). The GAD-7 showed a substantial effect of treatment, and all study outcomes showed significant effects of time. To be more precise, there was significant time by group interactions for the major outcome (PHQ-9) and two secondary outcomes (GAD-7 and SDS), showing that people who got pharmacogenomics-guided treatment improved more than those who received TAU. However, it's vital to recognize a few restrictions. First off, there is a chance of bias because this trial did not contain blinded assessor or prescriber outcomes. Secondly, it was not able to fully characterize participants' demographic and clinical characteristics using clinician-rated semi-structured measures, a greater number of women participated in this research. Furthermore, because this study was carried out in urban pharmacies, its findings might not apply to pharmacies in other places and communities. Lastly, not all DNA variants that could have changed gene activity were found by Pillcheck. In White patients and members of significant ethnic minority groups, only specific genetic variations were investigated [16].

A further Canadian study with 276 patients, was published in 2022. This 52-week, multicenter, three-arm, participant- and rater-blinded randomized controlled trial (RCT) assessed the clinical results of depression patients treated with combinatorial pharmacogenomics testing as opposed to therapy as usual (TAU). The study included patients who met the following criteria: they had to be at least eighteen years old, diagnosed with major depressive disorder (MDD) based on DSM-IV criteria, have a QIDS-C16 score of at least eleven at screening and a baseline QIDS-SR16 score of at least 11, and exhibit inadequate response to at least one psychotropic medication listed on the combinatorial pharmacogenomics report during the current depressive episode. At week eight, the primary finding was symptom improvement as measured by a change in the 17-item Hamilton Depression Rating Scale. Secondary objectives included remission (HAM-D17 ≤ 7) and response (≥50% decrease in HAM-D17). In comparison to TAU, patients in the guided-care arm show higher rates of remission (15.7% versus 8.3%), response (30.3% versus 22.7%), and symptom improvement (27.6% against 22.7%), but these changes were not statistically significant due to cohort size. The present investigation included various limitations. Using effect size estimates for symptom improvement (mean percent change in HAM-D17 score from baseline to week 8) from a previous open-label clinical trial of combinatorial pharmacogenomics testing, the statistical power and design of this trial were established. The following are additional restrictions on the trial: The majority of the cohort self-reported as "Caucasian," adherence was not assessed, the effect of poly-pharmacy on outcomes was not examined, and patients with no or mild depression were excluded from the per-protocol analyses, which resulted in different sample sizes for the Intention to treat and Per protocol populations [17].

This statistically not significant difference between pharmacogenomics-guided treatment and treatment as usual yielded from another two trials published by Perlis and Mccarthy in 2020 and 2021 respectively. In Perlis randomized controlled trial the participants (n = 304) were randomized to assay-guided treatment (AGT; N = 151) or treatment-as-usual (TAU; N = 153). Participants with a main diagnosis of nonpsychotic MDD, based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, MINI 7.0, and SIGH-D-17 score > 18 (i.e., moderate to severe depression), at both screening and baseline visits. In addition, according to the Antidepressant Treatment Response Questionnaire [ATRQ] criteria, participants had to have failed at least one prior satisfactory trial with a standard antidepressant for the present major depressive episode. At Week eight, the TAU group had significantly more people who had either not improved or had become worse (by at least one point on the SIGH-D- 17); 17/186 (9.1%) compared to 6/181 (3.3%) in the AGT group ($\chi 2 = 5.3$, df = 1, p =.021). When worsening was quantified as more than one, more than three, or more than five points above baseline, the results were comparable (p =.007, p =.02, and p =.037, respectively) [18].

To comprehend the discrepancy between randomized trials and cost-effectiveness results, more research is required. That's the reason more trials were conducted, in 2021, the McCarthy trial was published, with 182 patients with TRD, such as those suffering from PTSD, MDD, and BD. The subjects were randomized to receive either treatment as usual (TAU) or PGX-guided care, in which the physician made decisions based on PGX information.

And this trial supports the last trials' results. Although there was a tendency for PGX to improve more quickly than TAU, the overall difference was not statistically significant (p=0.08) (Table 4) [19].

Table 4: The Characteristics of Studies that Evaluate the Role of Pharmacogenomics Guided Treatment in Difficult-to-Treat Depression Cohort:

Author and year of publication	Mccarthy et al, 2021 [19].	Perlis et al, 2020 [18].	Tiwar et al, 2022 [17].	Papastergiou et al, 2020 [16].	Thase et al, 2019 [15].	Greden et al, 2019 [14].
Intervention studied	PGX-guided treatment and treatment as usual (TAU).	Pharmacogenomics guided versus standard antidepressant treatment.	Pharmacogenomics guided and as treatment usual (TAU).	Pharmacogenomics guided versus standard antidepressant treatment.	Pharmacogenomics guided and as treatment usual (TAU).	Treatment as usual (TAU) and pharmacogenomics guided intervention
Number of patients	182	304	276	213	912	1398
Type of study	RCT	RCT	RCT	RCT	RCT	RCT
Result/ Conclusion	The data reveal possible group differences in the utility of PGX testing in veterans with TRD.	Pharmacogenomics testing using a panel of pharmacokinetic and pharmacodynamics variants was not associated with significant improvement in the primary efficacy outcome when providers were unconstrained by the assay results.	The results indicate that combinatorial pharmacogenomics testing can be an effective tool to help guide depression treatment in the context of the Canadian health care setting.	Pharmacogenomics testing may be a valuable tool to allow pharmacists to more effectively collaborate in facilitating clinical treatment decision.	By identifying and focusing on the patients with predicted gene-drug interactions, use of a combinatorial pharmacogenomics test significantly improved outcomes among patients with MDD who had at least 1 prior medication failure.	Pharmacogenomics testing did not significantly improve mean symptoms but did significantly improve response and remission rates for difficult to treat depression patients over standard of care.

Linking the differential methylation to antidepressant treatment response:

The effectiveness of currently available antidepressants in treating major depressive disorder (MDD) is well established, however patient response varies widely. Although DNA methylation has shown to be a valuable biomarker in a variety of clinical settings, its significance for the mechanisms underlying the antidepressant response is yet unknown.

Eighty MDD patients were chosen for the Engelmann study. Utilizing the available genetic material, sorted into clear responders and age- and sex-matched non-responders (N = 40, each), depending on their antidepressant response after four weeks. Analysis of the early improvement after two weeks was carried out as a secondary goal. On the Illumina EPIC Bead Chip, DNA methylation was measured, and using the comb-p technique, differentially methylated regions (DMRs) were located. There were no significant differences in the epigenome methylation patterns associated with treatment response or early improvement. Twenty DMRs were linked to response; the strongest one was found in an enhancer area of SORBS2, which has been linked to type II diabetes and cardiovascular illnesses. CYP2C18, a gene previously connected to antidepressant response, had another DMR found in it. This study concludes a step toward personalized medicine, the relationship between differential methylation and antidepressant treatment response is gaining traction (Table 5) [20].

Table 5: The Characteristics of Studies that Evaluate Linking Differential Methylation to Antidepressant Treatment Response:

Author and year of publication	Engelmann et al, 2022 [20].
Intervention studied	Linking differential methylation to antidepressant treatment response
Number of patients	80
Type of study	RCT
Result/ Conclusion	To conclude, in a well-characterized MDD study group, we found differentially methylated areas linked with pharmacological antidepressant response prior to treatment initiation. Annotated to SORBS2, which has been previously characterized as an overlapping gene between mood disorders and obesity, was the DMR exhibiting the highest correlation.

Limitations:

There were restrictions on this systematic review when it came to finding pertinent papers to include. The studies present ranged in publication age between 2019 – 2023. Additionally, studies other than the English language, and whose data were not reliable for extraction and analysis were excluded from this systematic review.

Conclusion:

The most widespread mental illness in the world, major depressive disorder, also referred to as MDD is a substantial contributor to years spent disabled which has a large economic impact. The main goals for MDD treatment are long-term therapeutic effect maintenance and remission. Precision medicine has become an emerging force in healthcare along with the sequencing of the human genome and subsequent recognition of the genetic structures underlying many challenging illnesses. This systematic review identified the role of personalized medicine and pharmacogenomics testing in the response to antidepressants and antipsychotics. The effectiveness of genomic-guided care was variable in different age groups—the symptom improvement in previously failed treated MDD patients is still under the scope of many trials. The prediction of a patient's response to antidepressant medication may be made easier by differential methylation. This, therefore, meant that combinatorial pharmacogenomics testing has the potential to be a useful tool in directing the treatment of depression.

References:

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Impact of Pharmacogenomics Testing on Response to Antidepressants and Antipsychotics - A Systematic Review

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