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Evidence Basis for Pharmacogenetic Testing in Psychiatry

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ABSTRACT:

Mental illness constitutes a healthcare crisis of enormous proportions, and affects millions worldwide, leading to clinical and economic affliction. Patients respond to antipsychotics, antidepressants, and mood stabilizers with varying response and outcomes, and differential degrees of overall remission from schizophrenia, depression, and bipolar disorder. Pharmacogenetic testing has increasingly been incorporated in clinical workflows to enhance drug response through dosing and mitigating of adverse drug reactions. The Food and Drug Administration (FDA) has issued a set of drug-gene pairs for other psychotropic drugs that affect the cytochrome P450 pathway, including CYP2D6, CYP2C19 and CYP2C9 and HLA-A/HLA-B gene variants, which when genotyped lead to phenotypic correlation to poor metabolizers (drug dosages need to be increased), ultrarapid metabolizers (drug dosages need to be decreased) and normal metabolizers (extensive or wild-type); (receive standard drug dosing), and affect responses to psychotropic medications. Based on clinical data, the analytic validity and clinical validity and clinical utility have been established to improve upon the "trial and error" process that psychiatrists frequently use to prescribe the right drug in the right dosage for their patients. This review discusses the evidence basis for utilization and implementation of pharmacogenetic data that lead to robust outcomes in patients suffering from mental illness, and the validation established by studies in this growing area of research. The recommendation is that psychiatrics utilize pharmacogenetic information for providing accurate information on responses to psychotropic and antidepressant medications in the diagnosis and treatment of their patients to mitigate the "trial-and-error" process.

Keywords: pharmacogenomics, genetic variation, antidepressants, antipsychotics, mood stabilizers, psychiatry, drug-gene pairs, gene panels, machine learning methods

INTRODUCTION

The individual and socioeconomic impact of mental illness is associated with high costs ($2.5B USD in 2010) and has risen considerably[1]. Treatment of patients with mental health disorders has been dominated by trial-and-error methods that result in lack of treatment response and adverse side effects. The entry of pharmacogenetics, or pharmacogenomics into psychiatry, is a relatively novel phase in the clinical management of psychiatric patients. Pharmacogenetics involves the merging of pharmacology and genetics wherein patients undergo genetic testing to reveal interindividual variation for implementing the clinical efficacy of medications with less adverse drug reactions.[2] The clinical outcomes of precision psychiatry are to provide novel approaches for the diagnosis and prediction of mental health disorders and detection of biomarkers for individualized treatment [2,3,4,5]

Pharmacogenetics has traditionally been divided into two distinct fields: pharmacodynamics which is about the eliciting of drug effects, and pharmacokinetics which concerns absorption and metabolic and excretory pathways of a drug. [6] These two interrelated fields have led to divergent classification of drugs according to pharmacogenetics: pharmacodynamic (PD) genes, which lead to the development of drugs that affect medication response and their concomitant side effects, and pharmacokinetic (PK) genes, which lead to the development of drugs that affect medication metabolism[6].

The basis of pharmacogenetic testing is interindividual variation that ultimately affects the characterization of the PK and PD genes impacting the response of drugs. The impact of interindividual variation is significant: the efficacy of drugs is affected by their pharmacokinetics and pharmacodynamics profiles, which demonstrate interindividual variation whereby genetic variance affects drug plasma levels. A putative pharmacogenetic profile that demonstrates interindividual variation among patients has predictive value for determining therapeutic outcomes of PK and PD drugs utilized in the pharmacogenetic treatment of patients[6].

The evidence basis for assessing the value of PGx testing for managing psychiatric illnesses is determining how interindividual variation affects the clinical validity and clinical utility of the test [7-10]. The implementation of pharmacogenomics (PGx) is based on analytical validity (the testing reflects accurate genotype), clinical validity (the test has the ability to predict clinical outcomes) and clinical utility (the PGx test actually affects health outcomes and is thus prescribed by the clinician).

These aspects of testing are evaluated by innovative algorithms that collectively assess all these factors affecting implementation of a robust PGx test [8-11].

A robust PGx test is necessary for ensuring the safety and efficacy of drugs that are evaluated through randomized controlled trials, however these are arduous to perform in psychiatry due to temporal variations in drug response and difficulty in “blinding” the study to determine actual clinical efficacy. Most of the clinical validity and clinical utility of psychotropic medications have been established through retrospective and case-control studies and open-label studies that lead to data on real-world outcomes of the drug in certain patient populations. These studies form the foundation for establishing the evidence basis for the pharmacogenetic testing in psychiatry, which is conceivably built on uniformity in medication treatment and adjustment, consistency in therapeutic ranges of drugs, and trials indicating clear efficacy; i.e. a PGx study examining drug efficacy and determining which medication is appropriate for which type of patient based on biomarkers matched with particular genotypes, which forms the basis for constructing drug-gene pairs[12].

The development of biomarkers for matching drugs with genes and hence creating drug-gene

pairs for psychiatric medications has been evaluated by Malhotra et al., who hypothesize an ideal randomized clinical trial scenario whereby medication A has clinical effects for patients harboring a particular genotype while being ineffective for patients without the marker, with the opposite being the case for medication B (efficacious for the patients without the particular genotype)[12]. This scenario further envisions patients in early disease onset with baseline genotype that would be stratified according to genotype and randomized to two different treatments, with drug efficacy serving as the primary endpoint.

Other similar studies have been performed to establish evidence for pharmacogenetic testing for mental illness. However, these aspects of evidence basis for pharmacogenomic testing may be lacking in psychiatry for the most part, and this is further complicated by the necessity for studies that should include diverse ethnicities but currently do not; and the relative lack of medication adherence, which occurs in up to 72% in schizophrenic patients and leads to lack of robust data and less statistical power for detecting genotype-phenotype correlation accompanied by strong genetic biomarkers. [12].

A number of other factors characterizing medication administration in psychiatry complicate the development of robust PGx testing, leading to inconclusive results for establishing safety and efficacy for drug-gene pairs, and genotypic and phenotypic correlation for psychiatric drugs, and thereby impede the establishment of their clinical utility. A review conducted as early as 2012 on the clinical utility of medications for psychiatry implemented through pharmacogenetics and revealed that, while pharmacogenomics in psychiatry holds considerable appeal, the commercialization process and robust randomized clinical trials with large sample sizes randomized by genotype for psychiatric drugs are limited and meet with challenges. An ideal PGx study establishing evidence basis for the use of PGx testing in clinical practice would reveal drug-gene pairs through biomarker determination.

Other concerns remain, such as the typical cohort for clinical trials in psychiatry are chronically ill patients, who are often-times non-responsive and non-adherent, and carry co-morbidities such as substance abuse. Polypharmacy whereby many patients receive multiple medications is also an issue. All of these factors combine to produce increased data variance [12]. Head-to-head drug comparisons are also lacking which could be facilitated by PGx data, such as when a PM schizophrenic patient is isolated, a clinician may choose a medication metabolized by CYP2D6 such as quetiapine or ziprasidone, instead of risperidone or aripiprazole, but these clinical activities are not substantiated by prospective data that would test optional treatments prescribed based on predictive biomarkers [12].

Additionally, a study by Bousman et al found that consensus for aligning drug gene pairs with clinical decision support tools has yet to be reached. Gene panels include the major CYP2D6 and CYP2C19 alleles in testing panels, however, the majority of pharmacogenetic panels do not include both alleles. [13] Identifying risk of developing psychiatric disease and predicting response to treatment have revealed correlations between development of schizophrenia or bipolar disorder and response to antipsychotics and mood stabilizers, but research remains unclear on how specific therapeutic recommendations are facilitated. [14]

This article performs a literature review to evaluate the clinical utility of pharmacogenomic testing in psychiatry, with particular emphasis on antipsychotics and antidepressants, and evaluating their PK and PD effects to assess clinical utility of a robust PGx test and sufficiently addressing the challenges enumerated here. Genetic variation affects the efficacy and adverse event profile of psychotropic medication and is outlined. Pharmacogenomic testing has made significant inroads in determining drug efficacy and side effects for antipsychotics and antidepressant.

Mood stabilizers for the treatment of bipolar disorder have undergone investigation genome-wide association studies (GWAS), and associated loci with the disease are available for them. The overall recommendations are to call for more collaboration among pharmacists, implementation scientists, clinicians and industry to overcome these challenges in establishing clinical utility for pharmacogenetic tests; and for integrating gene panels in clinical decision support tools; as well as concluding with a discussion the novel use of machine learning tools for promoting PGx testing in the clinic for the purpose of mitigating the trial and error cumbersome process currently characterizing the typical mental health patient-provider encounter.

MATERIALS AND METHODS

The included terms "pharmacogenetic testing" AND "psychiatry" and "antidepressants" AND "pharmacogenomics" and "antipsychotics" AND "pharmacogenomics" and "mood stabilizers" AND "pharmacogenomics" were entered as Boolean operators and served as keywords in PubMed/MEDLINE databases to elicit reviews, meta-analyses, randomized controlled clinical studies, and systematic reviews for sources on the relevant themes and topics between the years 2016 and 2021 for this literature review. "Machine learning" AND "artificial intelligence" AND "psychiatry" also served as search criteria. Terms such as "alcoholism disorder" "epilepsy" and other neuropsychiatric diseases were excluded from this search strategy.

3. RESULTS

3.1 Antipsychotics

Schizophrenia affects 0.6-1.9 percent of the population, with the efficacy rate of 60-70% responding to antipsychotics, the standard of care for schizophrenics[16]. Typical and atypical antipsychotics are prescribed for schizophrenic and schizoaffective patients. The pharmacological mechanism of typical antipsychotics is dopamine 2 antagonism (blockade of dopamine receptors); atypical antipsychotics operate as dopamine 2 and serotonin 2A antagonists (5-HT2A, 2C and D2 receptor blockade) [16]. A meta-analysis indicated a SNP in the promoter regions of the DRD2 gene that influenced antipsychotic drug efficacy, in which instances of carriers had a deficient response rate (half to two-thirds) when compared to noncarriers [12]. SNPs have been characterized for the debilitating side effects of both typical and atypical antipsychotics such as aripiprazole, clozapine, risperidone, thioridazine, and olanzapine. Drug-gene pairs have been identified that are applied to drug labeling whose genotype leads to phenotypic correlation of poor metabolizers, ultrarapid metabolizers and normal metabolizers (wild-type), and affect responses to psychotropic medications. PMs for CYP2D6 include aripiprazole, (dosage reduce by ½) bexpiprazole (1/2 of normal dose), clozapine, iloperidone (1/2 of normal dose), perphenazine, pimozide (dosage should not increase to 4mg/day), and thioridazine (may lead to fatal cardiac arrhythmias when prescribed at the normal dose), and require reduced dosages upon administration in adults [16].

Yoshida and Muller conducted a review of literature on antipsychotic drug response and adverse effects to determine the clinical application of these medications in terms of both pharmacokinetic and pharmacodynamic profiles. They reported the results of candidate gene studies, GWAS and whole exome sequencing approaches that elucidated genes associated with antipsychotic response and antipsychotic-induced adverse effects and provided clinical recommendations (Table 1)[7]. Their findings are:

• A significant association was found between the serum concentrations of the second-generation antipsychotic olanzapine and CYP1A2*1D and *1F polymorphisms.

• Polymorphisms in CYP2D6, CYP1A2, and DRD3 affecting antipsychotic concentrations to some extent.

Additional studies also reported that there existed associations between polymorphisms of DRD2

and response to antipsychotics, "where three polymorphisms of DRD2 (rs180498, rs2514218, and rs1079597) were significantly associated with treatment response. In particular, rs2514218, which is located 47-kb upstream of the DRD2 gene, was previously reported as one of the genome-wide significant SNPs associated with risk of schizophrenia. Further, it was associated with response to antipsychotics such as clozapine and risperidone in independent samples."

Polymorphisms (including marker rs4680) of the COMT gene, the catechol-O-methyltransferase gene, another pathway related to dopamine degradation located on 22q11 chromosomal locus, was associated with response improvement particularly for clozapine. A "recent meta-analysis also showed that the COMT Val158Met (rs4680) polymorphism was significantly associated with response to antipsychotics. These findings suggest that COMT gene variants, particularly COMT Val158Met (rs4680), are associated with antipsychotic response."

Other studies implicated the serotonin 1A receptor (HTR1A) polymorphism rs6295 as being significantly associated with improvement in clinical symptoms.

GWAS identified the following single nucleotide polymorphisms (SNPs) as being significantly associated with treatment response:

- rs72790443: multiple EGF-like domains 10 (MEGF10),
- rs1471786: solute carrier family 1 member 1 (SLC1A1)
- rs12711680: contactin-associated protein-like 5 (CNTNAP5)
- rs6444970: TRAF2 and NCK-interacting kinase (TNIK)
- rs2133450, rs2069062, and rs2014195: GRM7
- rs9307122 and rs1875705: glutamate ionotropic receptor delta type subunit 2 (GRID2);
- rs3129996: protein phosphatase 1 regulatory subunit 18 (PPP1R18);
- rs6435681: erbb2 receptor tyrosine kinase 4 (ERBB4)

A GWAS with the largest sample sizes reported so far (n = 2,413 in the discovery cohort and n = 1,379 in the replication sample) identified in samples of Han Chinese ancestry patients five novel genome-wide significant loci associated with treatment response including:

- rs72790443 in MEGF10;
- rs1471786 in SLC1A1;
- rs9291547 in PCDH7, rs12711680 in CNT-NAP5,
- rs6444970 in TNIK.

Three additional loci were also found to be associated with SNPs indicating drug-specific treatment responses in antipsychotics, including:

- rs2239063 in CANCA1C for olanzapine
- rs16921385 in SLC1A1 for risperidone
- rs17022006 in CNTN4 for aripiprazole

3.1.1 Antipsychotic-induced side effects

Clozapine, a very effective drug for treatment-resistant schizophrenia, has the risk for the serious side effect of clozapine-induced agranulocytosis (CIA)/granulocytopenia. HLA (human leukocyte antigen) genes have been associated with this serious adverse event. The Clozapine-Induced Agranulocytosis Consortium (CIAC) demonstrated that two specific HLA alleles, HLA-DQB1 126Q and HLA-B 158T "were significantly associated with CIAG".[17] Clozapine-induced agranulocytosis occurs in up to 1% of schizophrenic patients medicated with clozapine. A GWAS implicated HLA-DQB1 667G>C for the risk of CA in carriers of this marker. A commercial test was relatively recently developed based on this evidence for determining the risk (low or high) of CA-onset but only had a sensitivity of 21.5%, limiting its clinical utility [6].

It has remained a long-standing goal of psychiatrics to utilize PGx tests to eliminate the blood surveillance of patients taking clozapine by determining a prognostic biomarker for

agranulocytosis. One such biomarker holding potential promise through a candidate gene study an allele at the HLA-DQB1 locus discovered in two small clozapine-treated cohorts (Figure 1). According to the data, the odds ratio reported was 16.86 (extremely high) and close to 90% of allele carriers progressed to agranulocytosis, but exhibited only 21% sensitivity (most individuals who develop agranulocytosis do not carry the allele) [12].

Table 1. Recommendations by various agencies for actionable gene pairs for antipsychotic drugs (adapted from Yoshida and Muller 2019).

	Drug labels with PGx information				PGx drug dosing guidelines (related biomarker)	CPIC level	PharmGKB level of evidence
	FD	EMA	HCSC	PMDA			
Aripiprazole	Actionable PGx	Actionable PGx	Actionable PGx	N/A	DPWG (CYP2D6)	B	CYP2D6 3
Aripiprazole lauroxil		N/A	N/A	N/A	N/A	N/A	N/A
Brexpiprazole	Actionable PGx	N/A	N/A	N/A	N/A	B	CYP2D6 N/A
Clozapine	Actionable PGx	N/A	N/A	N/A	DPWG (CYP2D6)	C D	CYP2D6 No literature support found for PGx HTR2C 2B
Haloperidol	N/A	N/A	N/A	N/A	DPWG (CYP2D6)	C	CYP2D6 3
Iloperidone	Actionable PGx	N/A	N/A	N/A	N/A	B/C	CYP2D6 3
Olanzapine	N/A	Informative PGx	N/A	N/A	DPWG (CYP2D6)	C D	CYP2D6 3 HTR2C 2B
Perphenazine	Actionable PGx	N/A	N/A	Actionable PGx	N/A	B/C	CYP2D6 N/A
Pimozide	Testing required	N/A	N/A	N/A	N/A	B	CYP2D6 4
Risperidone	Information PGx	N/A	Informative PGx	N/A	DPWG (CYP2D6)	B C D	CYP2D6 2A DRD2 2A HTR2C 2B
Thioridone	Actionable PGx	N/A	N/A	N/A	N/A	C	CYP2D6 3
Zuclopenthixol	N/A	N/A	N/A	N/A	DPWG (CYP2D6)	C	CYP2D6 3

Weight gain, a movement disorder called tardive dyskinesia, and agranulocytosis have been associated with the administration of antipsychotics. Carriers of the C allele of the rs3813929 polymorphism with a -759C/T substitution should avoid antipsychotics since a meta-analysis showed an association between the -795T allele and less weight gain [6]. This finding was substantiated by studies performed by De Luca et al published in 2007 of a “meta-analysis of eight studies demonstrated a doubling of risk for clinically significant (> 7%) weight gain from baseline associated with the C allele at this SNP.” Reynolds et al conducted a study on 123 schizophrenic Chinese patients who were antipsychotic drug-naïve. They revealed that a polymorphism in a promoter region (759 C/T in the 5-HT2C receptor gene) was associated with significant weight gain in these patients. Specifically, they found that the cohort with the T allele at this locus experienced much less weight gain, as opposed to the cohort with C allele at 6 and 10 weeks of drug administration. This effect was independent of the variable of gender and remained significant after excluding patients who were underweight or obese at baseline, and observed in patient taking risperidone or chlorpromazine. Additionally, none of the 27 subjects who harbored the T allele had severe weight gain according to the criteria, of >7%

increase from baseline body weight after a 6 weeks"[12].

Additionally, tardive dyskinesia occurs at a prevalence of 20-30% of patients taking antipsychotics, and is associated with the minor T allele of the taq 1A polymorphism: rs1800497 seems to have protective effects against TD and a SNP indicating substitution of methionine for valine at codon 158 associates with TD. These SNPs occur in "TD genes" harbored in D2 and D3 receptors and the catechol-o-methyltransferase enzyme.

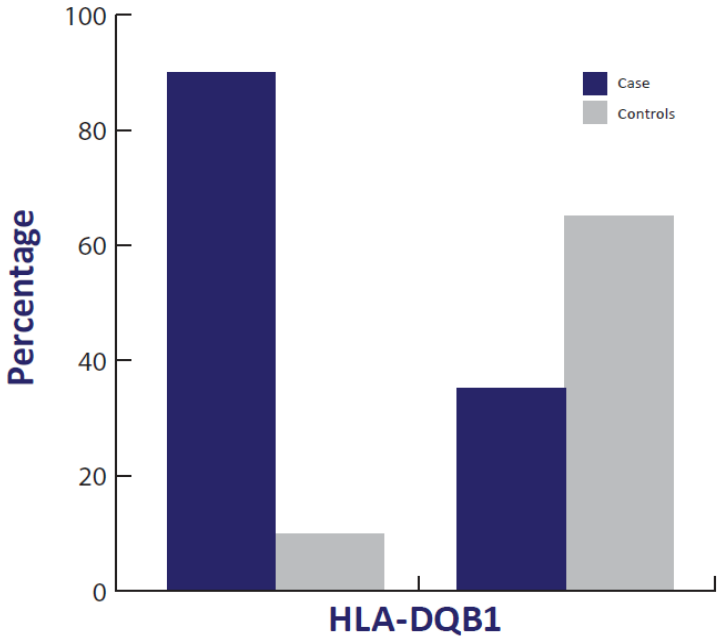

Figure 1. Proportion of agranulocytosis induced by clozapine in patient cases and controls with or without the HLA-DQB1 marker (Adapted from Malhotra et al).

3.1.2 Atypical antipsychotics

Atypical antipsychotics risperidone and aripiprazole are converted to their active metabolites, 9OH-risperidone and dehydroaripipr -azole, by the CYP2D6 enzyme. Patients were exposed to these antipsychotics to provide quantitative information on the effects of the CYP2D6 genetic variability on these two antipsychotics. This retrospective study evaluated patient data from a "routine therapeutic drug monitoring database at the Center for Psychopharmacology" in Norway between 2005 and 2018. Patients received risperidone or aripiprazole who had previously been genotyped for CYP2D6 variation and measured for drug and metabolite serum concentrations (pharmacokinetic criteria). The metabolic rate of conversion for both drugs served as primary endpoint, which was determined through an estimation of the metabolic ratios of drug to metabolite. Drug exposure measurement served as the secondary endpoint, and treatment failure as measured by switching to another antipsychotic was a third endpoint within a year after analysis. After analysis of the results, patients were categorized as PMs, NMs, and UMs and it was found that the metabolism of these drugs was significantly affected by CYP2D6 genotype, particularly in PMs that displayed close to 1.6X and 1.4X increase their metabolites when compared to NMs, resulting in decreased daily dosages when administered to PMs by about 19% (95% CI 5-35, p=0·010) and 15% (95% CI 1-28, p=0·033) respectively.

UMs, as well as PMs, were more likely to switch from risperidone to another antipsychotic, with ORs of 2.934, 95% CI 1·437-5·989, p=0·003 and 1·874, 1·128-3·112, p=0·015 respectively. However, this was not the case for aripiprazole, with a switching rate not significantly impacted by CYP2D6 genotype. The authors conclude that "CYP2D6 genotype had a substantial clinical effect on risperidone and aripiprazole exposure

and on the therapeutic failure of risperidone. Pre-emptive CYP2D6 genotyping would be valuable for individualizing risperidone and aripiprazole dosing and treatment optimization." [18]

3.2 Antidepressants

16.2% of the population had an episode of major depressive disorder in their lifetime. However, as shown by randomized controlled trials, remission occurs only in about 35-47% of patients treated with anti-depressants [19]. According to Rosenblat et al, pharmacogenomic testing can improve clinical outcomes by guiding medication response and tolerability when treating major depressive disorder (MDD). Pharmacogenomics promises to predict response to antidepressants through its increasing scalability and availability to the public, and has become scalable and available to the general public. [19] Menke et al also maintains that up to 50% of patients with depression are responsive upon the first dosages and 30% fail to respond with further treatment and medications. In addition to lack of efficacy, antidepressants also lead to adverse drug responses in 25% of patients. In both of these instances, genetic variants in the hepatic cytochrome P450 enzymes such as CYP2D6 and CYP2C19 have implicated drugs affecting pharmacokinetic and pharmacodynamic pathways[20].

In 2020, Hicks et al called for "clear and consistent communications regarding the role of pharmacogenetics in antidepressant pharmacotherapy," which consists of dissemination of drug-gene pairs with clinical utility such as those with genetic variation "predictive of poor metabolism(i.e. CYP2C19*2 and *3) [that] have significantly higher plasma concentrations and, conversely, those with genetic variants predictive of ultrarapid metabolism (i.e. CYP2C19*17) have significantly lower plasma concentrations."[21]

They add that patients taking brexpiprazole or vortioxetine receive specific dose reductions and also are who are known CYP2D6 PMs. Similarly, CYP2C19 PMs have recommended doses of 20 mg per day of citalopram according to the product label, while EM_S take the maximum recommended dose. However, they add that confusion still exists for administration of specific dosages of medication based on genotype-phenotype correlation as a result of lack of clear communication[21].

Approximately 50 years ago, studies showed "strong evidence" the connection between pharmacokinetic distinctions and certain genotypes. Examples include amitriptyline with CYP2D6 and CYP2C19; sertraline and citalopram [SSRIs] with CYP2C19; moderate evidence for mirtazapine (tetracyclic AD), venlafaxine (SSNRI) with CYP2D6; low levels of evidence for bupropion (SNDRI) with CYP2B6.[6]

One gene has been implicated in pharmacological response to antidepressants: the serotonin transporter gene, or SCL6A4. This locus for this gene is chromosome 17q, and leads to reuptake of 5HT into presynaptic neurons. [6]

A SNP was discovered in the upstream promoter region of this gene, 5-HTTLPR, which is located 10,000 base pairs from the transcriptional start site. An indel of 6-8 units produces "a short allele that is 44 bp shorter than the long allele."[6] Interindividual alterations of this gene leads to genomic variation in antidepressant response. The short variant associates with responses in 50% of Caucasians, whereas Asian populations harbor the long variant, and associates with more robust responses to antidepressants. However, it is not as prevalent as the short allele, which occurs in 75% of Asians. [16]

Two meta-analysis were conducted to analyze the association of antidepressant responses various populations but have led to conflicting results. A meta-analysis of 15 studies revealed that the long allele homozygotes in European ancestry populations display more consistent responses to SSRIs, while another analyzed 28 studies conducted on various ethnicities showed "there is not significant effect on the transporter length polymorphism on rates of antidepressant responses." It was concluded that confounding

variables were responsible for these results in form the of "heterogeneity of effect sizes" and "interacting factors" that could not find a direct association between the polymorphisms of the transporter gene and response to antidepressants. [16]

Other polymorphisms of the SLC6A4 gene could also explain variation in therapeutic effects. It has been shown that response to fluoxetine treatment associates with the rs25531 SNP, also located in the upstream region of the gene. In fact, it has been surmised that these two polymorphisms located in the upstream region are in linkage disequilibrium. (r2 = 0.75) since the G allele of the rs25531 SNP and the long allele of the SLC6A4 gene associate with lower drug response, as well as the A allele of the SNP and the short allele of the gene.

Other serotonin receptors have been implicated in antidepressant response. A SNP located in the 5-HT 1A receptor also in the promoter region, C-1019G, confers variable response of antidepressants with the G allele (p=0.049). The combination of this SNP and variation in the SLC6A4 was found to be a "risk genotype" leading to lower rates of remission as found in a study of 130 patients on SSRI followed over 12 weeks (p=0.009). Another SNP in the 5-HT 1 A receptor gene, rs7997910, was analyzed in a study of 1953 patients treated with citalopram. The results indicated an "18% absolute risk of having no response" in patients harboring the homozygous allele. Additionally, African-Americans show less effective response to treatment possibly due to the A allele of the rs7997910 SNP occurring at less frequency than white participants. Drugs that have CYP2D6 as a biomarker indicating PMs are amitriptyline, clomipramine, doxepin, duloxetine, escitalopram, fluoxetine, imipramine, nefazodone, nortriptyline, paroxetine, protriptyline, trimipramine, venlafaxine, and vortioxetine.[16]

However, progress has occurred, particularly for antidepressants. For instance, the antidepressant mirtazapine has been shown to be more effective than selective serotonin reuptake inhibitors, or SSRIs, by promoting both serotonergic and noradrenergic response. In 15 randomized studies analyzed through a meta-analysis comparing remission rates and time to remission for mirtazapine (n=1484) and SSRIs (n=1487] across "6 weeks of double-blinded therapy" (accompanied by repeated analysis for eight studies over at least 8 weeks), data revealed that the mirtazapine cohort had higher remission rates with statistical significance when compared with the SSRI cohort "after 1 (3.4 vs. 1.6%, P = 0.0017), 2 (13.0 vs. 7.8%, P<0.0001), 4 (33.1 vs. 25.1%, P<0.0001), and 6 weeks (43.4 vs. 37.5%, P = 0.0006) of treatment." [15]

Additionally, the mirtazapine cohort demonstrated a "74% higher likelihood for achieving remission, particularly during the first 2 weeks therapy." The findings implicate a much greater efficacy for mirtazapine over SSRIs[15]. Findings shown by these studies demonstrate real promise for providing evidence basis in the treatment of depression, and perhaps point to innovative treatments over standard-of-care.

A systematic literature review was conducted by Solomon et al to determine if CYP2D6 and CYP2C19 have predictive value in predicting response to antidepressants and adverse drug events to ameliorate clinical outcomes, thus generating evidence base for pharmacogenomics when prescribing antidepressants. Studies from 2013 to 2018 were included in the analysis, of which sixteen were considered relevant. However, the results were inconclusive, yielding findings that genotype testing of CYP2D6 and CYP2C19 has variable outcomes, and may only "predict response in certain individuals." The authors call for "[r]andomized, controlled, prospective trials with adequate sample sizes would best clarify whether genotype-guided antidepressant selection will ultimately improve clinical outcomes", which are detailed below. [22]

Another systematic review was conducted, but also with inconclusive findings. 66 records were identified assessing MDD outcomes of

antidepressants and their cost-effectiveness through critical examination. One study details an industry-sponsored randomized, double blind prospective trial over a 12-week period that showed 2.5 increased remission rates in a guided dose group. Another industry-sponsored trial was also conducted however it was unblinded and lacked a control group, and showed improvement in clinical outcomes. Another study detailed utilizing the commercial test GeneSight, and is discussed in more-depth later. The authors conclude that these results indicate a level of promise for pharmacogenetic testing but determining cost-effectiveness and better health outcomes is "not yet supported with replicated evidence." [19]

3.2.1 Determining Serum Concentration-Clinical Response Associations

A pharmacokinetic study was conducted on the antidepressant duloxetine, which inhibits reuptake of both serotonin and norepinephrine, to determine the recommended doses for the antidepressant as a function of serum concentration. 66 MDD patients were administered a daily dosage of duloxetine of 60 mg/day as monotherapy on an outpatient basis and were monitored for three months. Hamilton Depression Rating Scale-21 (HAMD-21) was conducted at baseline, month 1 and month 3 to determine antidepressant response. It was found that the serum concentration displayed "high inter-individual variability" in the patient population, with a linear correlation between serum concentration in the range of 30-120 ng/mL with duloxetine observed, along with a "strong association between [serum concentration] and [antidepressant response] following a bell-shaped function at month 1 and at month 3."[23]

These results led the study authors to conclude that a poor clinical response associated with subtherapeutic serum concentration, which progressively decreased at higher concentrations. However, at the recommended dosage (30-120 ng/mL), maximal drug efficacy was observed. The authors surmised that this was due to the "optimal saturation of both serotonin and norepinephrine transporters" and then proceeded to suggest that determination of serum concentration could help guide clinicians to prescribe the optimal treatment of duloxetine for the best antidepressant response rate. [23]

A similar study was conducted by Florio et al, however with the antidepressant escitalopram investigated, which is considered first-line treatment. Serum concentration of escitalopram and antidepressant response (AR) was tested for clear association by following 70 MDD patients for three months treated with escitalopram monotherapy. HAMD-21 was also employed to assess symptoms at baseline, month 1 and month 3 of antidepressant response. Results showed an association at month 1 ($p<0.001$) and month 3 ($p=0.0003$), however these associations did not persist at lower therapeutic thresholds. The association between serum concentration and response followed "a nearly-asymptotic function, with poor AR at sub-therapeutic [serum concentrations of escitalopram] and stable [antidepressant response] at therapeutic [serum concentrations]. Thus, when a patient reaches the therapeutic [serum concentration] range, further increase of escitalopram dosage seems to be useless [24].

Trials supporting clinical utility of pharmacogenomics tests for antidepressants

In the GUIDED trial (Genomics Used to Improve DEpression Decisions), 1167 patients with treatment resistant MDD were randomized to pharmacogenomics-guided intervention and treatment as usual. The trial constituted a patient-blind randomized control trial with a rater, unlike many other studies eliciting clinical utility for PGx testing in psychiatric patients. Clinicians however could view the pharmacogenomic test results to offer information on medication selection, or guided care. The drugs were categorized as "use as directed" or "use with caution" considered congruent with test results, or "use with increased caution" [with additional surveillance], considered incongruent with test

results. Patients were unblinded after 8 weeks and were evaluated at that point through the 17-item Hamilton Depression Rating Scale (HAM-D17)] to elicit the results of primary endpoint of symptom improvement. The authors reported relatively promising results: improvements in response (26% vs 19.9%, p=0.13) and significant remission (28.5% vs 16.7%, p=0.036), even though symptom improvement was not significantly different when compared to treatment as usual (27.2% versus 24.4%, p=0.107). The authors concluded that "[p]harmacogenomic 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" [25] (Figure 2).

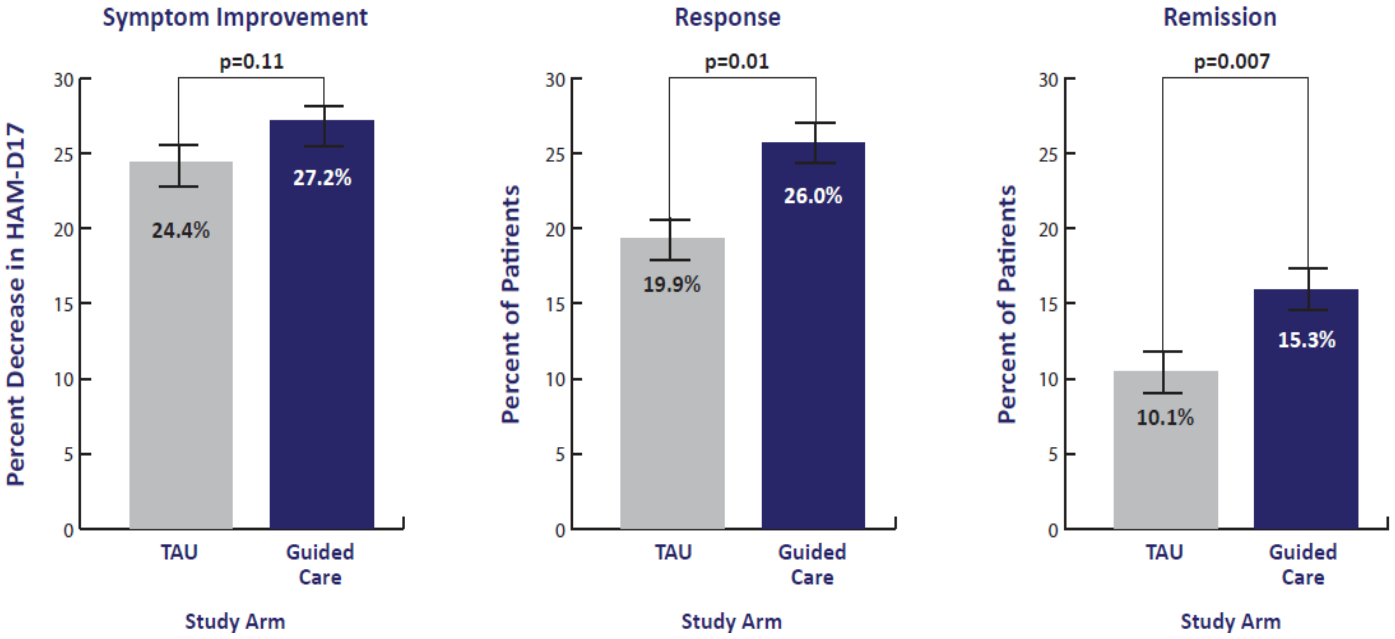

Figure 2. "Patient outcomes at week 8 in the pharmacogenomics guided-care arm (n=560) com-pared to treatment as usual (n=607). Outcomes were evaluated using the HAM-D17 depression rating scales." (Adapted from Greden et al, 2019).

A similar rater, pharmacogenomics-guided trial was conducted by Bradley et al on depressed patients with the co-morbidity of anxiety in different clinical settings and compared with standard of care [26]. 685 patients enrolled in a prospective, randomized study design in a rater-blinded approach and were evaluated by psychiatrists, internists and obstetric-gynecologists and family medicine practitioners. In this study, a panel of ten genes harboring

genetic variants, the NeuroIDgenetix test, was utilized to direct medication management recommendations based on "gene-drug and drug-drug interactions for over 40 medications used in the treatment of depression and anxiety." Also, in this study the HAM-D17 (along with the Hamilton Rating Scale for Anxiety (HAM-A)) determined pharmacogenetic testing conducted at the first visit for screening and at baseline. The patients enrolled and were randomized to the control group receiving standard of care, and the experimental cohort from which pharmacogenetic results were generated to assist clinicians with guided medication selection. According to the authors, they conducted HAM-D17 and HAM-A assessments at 4 weeks, 8 weeks, and 12 weeks after baseline in order to evaluate drug selection according to their efficacy. In depressed patients, response rates and remission rates were robust: (p = 0.001; OR: 4.72 [1.93-11.52];p = 0.02; OR: 3.54 [1.27-9.88]). Significantly, the group who received pharmacogenetics guidance experienced these outcomes. Additionally, patients in the experimental cohort who had a diagnosis of anxiety demonstrated relatively higher HAM-A scores at both 8 and 12 weeks, (p = 0.02 and 0.02, respectively), accompanied by higher response

rates. (p = 0.04; OR: 1.76 [1.03-2.99]), [and they concluded] "that pharmacogenetic-guided medication selection significantly improves outcomes of patients diagnosed with depression or anxiety, in a variety of healthcare settings"[26].

CYP2C19 has also undergone pharmacogenomic investigation for evaluating the efficacy and adverse events of the antidepressants citalopram and escitalopram. CYP2C19, much like CYP2D6, also has genetic variants associated with PMs, NMs and UMs defined by SNPs in CYP2C19 rs4244285 and rs12248560. In a meta-analysis conducted by Fabbri et al, it was found that these polymorphisms were genotyped when analyzing genome-wide data from escitalopram and citalopram-treated samples in STAR*D, GENDEP, GenPOd, and PGRN-AMPS. Efficacy was measured by remission and symptom improvement, with adverse events revealed at weeks 2-4, 6 and 9 in three samples. PMs displayed superior improvement in symptoms and higher rates of remission (OR = 1.55, CI = 1.23-1.96) when using NMs as a reference. However, side effects were greater in the PM group, including at 2-4 weeks, higher risk of both gastrointestinal and neurological symptoms; (OR = 1.26, CI = 1.08-1.47; OR = 1.28, CI = 1.07-1.53, respectively). Weeks 6 and 9 were similar between PMs and NMs. PMs risk of dropout was about equivalent to NMs, also accompanied by similar dosing. The study authors conclude that "CYP2C19 polymorphisms may provide helpful information for guiding citalopram/escitalopram treatment, despite PMs being relatively rare among Caucasians (~2%)"[27].

A similar study also evaluating escitalopram was conducted by Jukic et al, who determined in a large patient population who were CYP2C19-genotyped (n=2087) after exposure and treatment failure. 4228 escitalopram concentration measure-ments were collated on these patients retrospectiv -ely from a drug-monitoring database. This population was further stratified based on CYP2C19 genotype: Their results:

• The CYP2C19Null/Null group had significantly higher escitalopram serum concentrations in comparison to the CYP2C19*1/*1 group. Specifically, the concentrations were 3.3 fold higher. In the CYP2C19*Null/*1 group and the CYP2C19Null/*17 group serum concentrations were 1.6 fold and 1.4 fold higher, respectively The CYP2C19*1/*17 group experienced a 10% decrease in escitalopram serum concentrations, while the CYP1C19*17/*17 group had a 20% decrease..

• CYP2C19Null/Null, CYP2C19*1/*17, and CYP1C19*17/*17 groups were switched from escitalopram to another antidepressant within a year at 3.3, 1.6, and 3.0 times more frequency when compared to the CYP2C19*1/*1 group.

The study authors concluded that genotyping escitalopram-treated patients and assessing CYP2C19 genotype "had a substantial impact on exposure and therapeutic failure of escitalopram, as measured by switching of antidepressant therapy. The results support the potential clinical utility of CYP2C19 genotyping for individualization of escitalopram therapy." [28]

A systematic review and meta-analysis of prospective, randomized controlled trials assessed pharmacogenetic-guided decision support tools to determine symptom remission on MDD. Out of a cohort of 1737 patients, the five RCTs assessed showed that pharmacogenetic-guided therapy utilizing these decision support tools for 887 MDD patients had superior symptom relief compared to the 850 MDD patients receiving TAU.[29]

Two randomized control studies provided replicative evidence for the clinical utility of a combinatorial five gene test that was accompanied by GeneSight, an "integrated, multigenetic pharmacogenomic testing platform" for managing psychotropic medications for treating MDD patients in the outpatient setting. [30,31]. MDD patients were randomized to treatment as usual (TAU) (n=25) or a "pharmacogenomic-informed GeneSight (n=26) arm." The cohorts were blinded to which treatment arm they were in, and their

symptoms (depression severity evaluated by HAMD-17, PHQ-9, QIDS-SR, QIDS-CR) "was assessed by blinded study raters." After enrolling in the study for a period of 2 days, the clinicians for the guided group were given the GeneSight interpretive report that matched the 26 medications under evaluation to "bins", green, yellow, or red, according to the subjects's PK and PD "combinatorial gene variant profile." [28]. The blinded study raters then determined the depression severity according to the measurement scales mentioned above at 4, 6, 10 weeks post-baseline measurements. It was found that the GeneSight arm had superior improvement in depressive symptoms on HAMD-17 at 10-week point over TAU (30.8% vs 20.7%; p=0.28). TAU patients in the red bin indicated by medications administered that were contraindicated according to their genotype experienced no mitigation of their symptoms, as "measured by HAMD-17 at week 10, which was far less than the 33.1% improvement (p=0.06) in the pharmacogenomic-guided subjects also receiving a red bin medication (26.4%)." According to Winner et al, "[p]harmacogenomic-guided treatment with GeneSight doubles the likelihood of response in all patients with treatment-resistant depression and identifies 30% of patients with severe gene-drug interactions who have the greatest improvement in depressive symptoms when switched to genetically suitable medication regimens."[28]

A similar study was performed that had similar methods and results, and also evaluated the potential benefit of this medication regimen and the use of GeneSight. This study replicated the findings and showed that depression outcomes were "significantly improved" when using GeneSight. This open-label study randomized outpatient patients to unguided (n=113) and guided groups (n=114), and their depression sever -ity was also measured at certain time points by the 17-item Hamilton Rating Scale for Depression (HAMD-17), the Quick Inventory of Depressive Symptomatology - Clinician Rated (QIDS-C16), and the Patient Health Questionnaire (PHQ-9), which "were collected at baseline, and at 2, 4, and 8 weeks." [31]. They also found that the guided group exhibited improvement in depression severity using all the measures (HAMD-17, $P < 0.0001$; QIDS-C16, $P < 0.0001$; PHQ-9, $P < 0.0001$) compared with the unguided group.

Response rates and remission rates were also higher in the guided group over the unguided arm at week 8 (HAMD-17, $P = 0.03$; QIDS-C16, $P = 0.005$; PHQ-9, $P = 0.01$). Similar to Winner et al, these investigators also observed that "[p]articipants in the unguided group who at baseline were prescribed a medication that was most discordant with their genotype experienced the least improvement compared with other unguided participants (HAMD-17, $P = 0.007$)."[31]

In another randomized control trial, 316 MDD adult patients were enrolled to generate evidence for recommending PGx testing to guide drug therapy. 18 Spanish public hospitals participated, and recruited this cohort for genotyping through the Neuropharmagen commercial PGx panel which were further stratified according to guided treatment (n=155) or TAU (n-161). The group utilized a "computer-generated random list that locked or unlocked psychiatrist access to the results of the PGx panel depending on group allocation." Both patients and interviewers collecting the depression algorithms were blinded in terms of group allocation.

Results:

• At the end of the 12 week follow-up period, 288 patients remained for analysis. "(n = 136, TAU n = 144). A difference in sustained response served as the primary outcome in the study and was not met. However, the cohort that received PGx guided treatment experienced a higher responder rate when compared to TAU when evaluated at 12 weeks (47.8% vs 36.1%, $p = 0.0476$; OR = 1.62 [95%CI 1.00-2.61]). This robust observed difference remained significantly higher even after patients were removed from this PGx-guided group when the test recommendations were not explicitly reported by clinicians. (51.3% vs 36.1%, $p = 0.0135$; OR = 1.86 [95%CI 1.13-3.05])."

• The consistent effects were more pronounced in patients from 1 to 3 failed drug trials. Furthermore, in term of adverse events burden at baseline, the odds of achieving improved tolerability as measured by Frequency, Intensity and Burden of Side Effects Rating Burden subscore ≤2 were higher in the PGx-guided group when compared to the control cohort at 6 weeks, and persisted at 12 weeks (68.5% vs 51.4%, p = 0.0260; OR = 2.06 [95%CI 1.09-3.89]).

The study authors concluded "PGx-guided treatment resulted in significant improvement of MDD patient's response at 12 weeks, dependent on the number of previously failed medication trials, but not on sustained response during the study period. Burden of side effects was also significantly reduced." [32]

3.3 Mood Stabilizers

A few literature reviews were conducted as early as 2013 to investigate the adverse events of bipolar patients taking carbamazepine, a seizure medication that has a secondary indication in the treatment of bipolar disorder. The human leukocyte antigen B (HLA-B), "a gene that encodes a cell surface protein involved in presenting antigens to the immune system," has been implicated. One variant allele the HLA-B*15:02 has an association "with an increased risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in response to carbamazepine treatment." [33] Currently, the Food and Drug Administration recommends that "patients with ancestry in at-risk populations should be screened for the presence of HLA-B*15:02 allele prior to starting carbamazepine," since there are instances of carbamazepine-induced SJS/TEN, that usually occurs in the first 3 months of drug administration. Evidence has accumulated linking HLA-B*15:02 to SJS/TEN. In Table 2, therapeutic recommendations for carbamazepine dosing are detailed for patients taking carbamazepine and are genotyped for HLA-B*1502 [33].

Table 2. Therapeutic recommendations for carbamazepine dosing and genotype (Adapted from Leckband et al 2013).

Genotype	Phenotypic Implications	Therapeutic recommendations	Classification of recommendations[a]
Noncarrier of *HLA-B*15:02*	Normal or reduced risk of carbamazepine-induced SJS/TEN	Use carbamazepine per standard dosing guidelines	Strong
Carrier of *HLA-B*15:02*	Increased rish of carbamazepine-induced SJS/TEN	If patients is carbamazepine-naive, do not use carbamazepine[b]	Strong
		If patient has previously used carbamazepine for longer than 3 months without incidence of cutaneous adverse reactions, cautioously consider use of carbamazepine	Optional

Two GWAS were conducted to determine variation in response to lithium treatment in bipolar disorder and elicit the discovery of genetic biomarkers [34]. 2563 patients from 22 international sites from the International Consortium on Lithium Genetics (ConLiGen) participation in data collection to determine SNPs for "categorical and continuous ratings of lithium response" Four linked SNPs on a single locus on chromosome 21 were isolated that had genome-wide significance "rs79663003, p=1·37 × 10(-8); rs78015114, p=1·31 × 10(-8); rs74795342, p=3·31 × 10(-9); and rs75222709, p=3·50 × 10(-9))", and associated with response to lithium that also harbored two genes for long, non-coding RNAs: AL157359.3 and AL157359.4. These long, noncoding RNAs are implicated in gene regulation in the nervous system. This study authors concluded that "[l]ncRNAs are increasingly appreciated as important regulators of

gene expression, particularly in the central nervous system (CNS). Confirmed biomarkers of lithium response would constitute an important step forward in the clinical management of bipolar disorder. Further studies are needed to establish the biological context and potential clinical utility of these findings." [34]

In an extensive multi-authored study, GWAS was conducted on schizophrenic patients to elicit a polygenic score to determine if there is an association with lithium treatment responders in bipolar patients, along with evaluation any molecular basis for it. According to the authors, the response to lithium was "defined on both the categorical and continuous scales using the Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder score. The effect measures include odds ratios and the proportion of variance explained." Polygenic scores were determined for 36,989 individuals afflicted with schizophrenia, as well as data on genotype from 2586 bipolar patients who had been treated with lithium between 2008 through 2013 to assess long-term responders from the Consortium on Lithium Genetics. They found that the polygenic score for schizophrenia "was inversely associated with lithium treatment response in the categorical outcome". 15 genetic loci were found to possibly overlap with lithium treatment response and susceptibility to schizophrenia, and "[f]unctional pathway and network analysis of these loci point to the HLA antigen complex and inflammatory cytokines." Overall, the authors concluded that their study provides evidence basis for understanding how a poor response to lithium in bipolar patients had a negative association with high genetic load for schizophrenia, and could provide impetus for future studies examining "the potential for translational research aimed at personalized pre-scribing of lithium." [35]

3.4 Drug-Gene Pairs Relevant To Psychiatry

Fan and Bousman conducted an analysis of commercial genetic tests that test for drug-gene pairs in psychiatry. These tests are based on dosing guidelines issued by Clinical Pharmacogenetics Implementation Consortium (CPIC) and Pharmacogenomics Knowledge Base (PharmGKB); "gene-drug pairs included on 22 commercial pharmacogenetic test panels were extracted and cross referenced with 74 drug gene pairs with dosing guidelines in [PharmGKB]," with a focus on drug-gene pairs in psychiatry. They found that 28% of these tests were covered by the tests under examination. (Table 3): "[o]n average 80% (SD = 15%; range 39-100%) of the 28 drug-gene pairs were covered by the test panels examined." These include (CYP2D6-venlafazine, CYP2D6-paroxetine; CYP2D6-amitriptyline; CYP2C19-sertraline; CYP2C19-citalopram; CYP2C19- amitriptyline), echoing the review by Ehret. The conclude that these commercial tests panels show relevance, possibly having clinical utility (not assessed in this study) and are "well-equipped to facilitate implementation" of the dosing guidelines implicated in psychiatry[36].

Table 3. Drug-gene pairs in psychiatry (adapted from Fan and Bousman 2020).

Gene	Drug
CYP2C19	Amitriptyline, citalopram, clomipramine, doxepin, escitalopram, imipramine, sertraline, trimipramine,
CYP2D6	Amitriptyline, aripiprazole, atomoxetine, clomipramine, desipramine, doxepin, fluvoxamine, haloperidol, imipramine, nortiptyline, paroxetine, trimipramine, venlafaxine
CYP2C9	phenytoin
HLA-A	Carbamazepine
HLA-B	Carbamazepine, oxcarbazepine, phenytoin

Table 4. Medication recommendation agreement by drug class and decision support tool pairs (adapted from Bousman and Dunlop 2018).

Drug class DST pairs	Maximum possible agreements	Observed agreements	Expected agreements by chance	% Agreement	Cohen's kappa[a]	95% CI	Max kappa	Corrected kappa
Antidepressants								
GeneSight–Genecept	110	73	55.4	66%	0.322	0.00-0.49	0.835	0.386
GeneSight–CNSDose	90	42	39.1	47%	0.063	0.00-0.24	0.258	0.2443
GeneSight–Neurophamagen	95	62	47.3	65%	0.307	0.11-0.50	0.727	0.422
Genecept–CNSDose	90	41	40.6	46%	0.007	0.00-0.19	0.291	0.024
Genecept–Neurophamagen	100	58	50.0	58%	0.160	0.00-0.35	0.840	0.190
CNSDose–Neurophamagen	85	46	44.1	54%	0.046	0.00-0.33	0.389	0.118
Overall (antidepressant)	570	322	280.8	56%	0.142	0.00-0.22	0.7303	0.195
Antipsychotics								
GeneSight–Genecept	85	42	43.3	49%	0.000	na[b]	na[b]	na[b]
GeneSight–Neurophamagen	55	34	27.8	62%	0.227	0.00-0.49	0.963	0.236
Genecept–Neurophamagen	60	33	31.8	55%	0.043	0.00-0.31	0.468	0.092
Overall (antipsychotics)	200	109	106.4	55%	0.028	0.00-0.18	0.925	0.030
Anxiolytics & hypnotics								
GeneSight–Genecept	60	33	31.0	55%	0.069	0.00-0.33	0.552	0.125
GeneSight–Neurophamagen	30	22	15.0	73%	0.467	0.00-0.78	0.468	0.539
Genecept–Neurophamagen	30	12	16.3	40%	0.000	na[b]	na[b]	na[b]
Overall (Anxiolytics & hypnotics)	120	67	63.8	56%	0.057	0.00-0.25	0.875	0.065
Mood stabilizers								
GeneSight–Genecept	20	14	13.6	70%	0.063	0.00-0.69	1.000	0.063
GeneSight–Neurophamagen	20	18	14.8	90%	0.615	0.11-1.00	0.615	1.000
Genecept–Neurophamagen	35	31	29.5	89%	0.278	0.00-0.94	0.639	0.435
Overall (mood stabilizers)	75	63	57.6	84%	0.312	0.00-0.67	0.771	0.405
Overall (All drug classes)	**965**	**561**	**481.6**	**54%**	**0.164**	**0.10-0.23**	**0.830**	**0.198**

Bousman and Dunlop conducted a study performing a comparison through cross-sectional methods of four available decision support tool (DST) panels available to providers: CNSDose, Genecept, GeneSight, and Neuropharmagen), with a cohort of five treatment-resistant patients without psychosis undergoing treatment in the Mood and Anxiety Disorders Program at Emory University School of Medicine. The goal was to determine genotype and phenotype agreement among the platforms in pairs, and whether there were any consistencies (or inconsistencies) in medication recommendations. They found 7 of each pharmacokinetic and pharmacodynamic genes were present in two or more panels, which included CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, and UGT2B15; and BDNF, COMT, HLA-A, HTR2A, HTR2C, OPRM1, and SLC6A4 respectively, leading to assessment of agreement in genotype and phenotype. CYP2C9 featured prominently in their results as having 100% agreement across all panels according to both genotype and phenotype. Additionally, CYP2C19, CYP3A4 and UGT2B15 had "perfect genotype agreements", but "phenotype agreements ranged from 33-89%." In contrast, CYP2B6 showed complete phenotype agreement across all DSTs, accompanied by 73% genotype agreement. All PD genes displayed 100% genotype and phenotype agreement, with the exception of SLC6A4 (47% genotype agreement; 20% phenotype agreement). Medication recommendation agreements were also assessed, resulting in 24 antidepressants, 18 antipsychotics, 12 anxiolytics/hypnotics, and seven mood stabilizers appearing on two or more DSTs, and "were compared across the five participants, resulting in 965 total medication recommendation comparisons. Within each drug class, the level of agreement varied depending on the DST pair being assessed but agreement between any two DSTs rarely exceed 70%, with

the exception of mood stabilizer recommendations" (Table 4). The finding of jointly flagged actionable medication recommendations in two or more DSTs pairs occurred at 26% (n=250), however 19% of 47 of these recommendations were in disagreement over dosing and had relatively random distribution across the DST pairs (range = 0–100%) or drug classes (range = 11–75%)[37].

Battig et al call for "interdisciplinary exchange" between pharmacists and psychiatrists to reduce hospitalization stays through the implementation of guided intervention through a commercial gene panel by Humatrix AG. In a retrospective study, the length of hospitalization and metrics of medication management (medication prescribed, days spent increasing the dose after genotyping, changes to medication due to ADR; therapeutic monitoring before and after genotyping); and quality indicators such as Becks Depression Inventory II and Global Assessment of Functional Scale were evaluated for an intervention cohort (n=49) and control group (n=94). The investigators found that the intervention arm and control group had "significant differences" in length of stay (36.3 days vs 46.6 days (SD 19.3) (Figure 3). Additionally, the intervention group experienced delayed treatment of AD treatment when compared with the control group. Further, in treatment-naïve patients, the improvement rate for both Beck Depression Inventory (BDI-II) and (Global Assessment of Functioning) GAF was greater for the intervention group (Table 5). They conclude that "PGx testing in patients suffering a MDD appears to limit a patient's time spent in a psychiatric clinic if the testing is conducted early in the stay…A pharmacist on the ward can facilitate the process of interpreting the genotype results and develop a recommendation for a first-choice treatment. The cooperation of physicians and the pharmacist and thus, the interdisciplinary approach also contributes to the results of this analysis." [6].

Other concerns have emerged for the interpretation and the genotype to phenotype translation of pharmacogenomic tests through clinical decision support tools. These processes have been reported to be fraught with inconsistency and lack standardization. Many patients are prescribed medications that also affect cytochrome P450 as well and generate phenocopying for psychotropic medications, whereby an NM is converted to an intermediate metabolizer, or an UM is converted to an NM. Further, many studies are biased for populations with European ancestry. A review by Bousman et al 2021 presented information in allelic frequencies across ancestry groups for metabolic enzymes affected by psychotropic drugs and illustrates these allelic frequencies among these groups; one example being the CYP2D6*29 with decreased function allele that has a 0.1% frequency in European ancestry populations (relatively uncommon) but a 9% allelic frequency in African-American populations, thus being more prevalent. However, many clinical decision support tools default to the European ancestry populations when providing pharmacogenomic information leading to "inadvertent assignment of these alleles [which] could lead to inaccurate metabolizer phenotype predictions (e.g., assigning a person as a NM when they are an IM). Thus, a "normal" genotype result for an individual, particularly those of non-European ancestry, should be interpreted in the context of the alleles that were tested to avoid potential inappropriate medication selection or dosing decisions." [38]

The availability, affordability and acceptability of testing along with the turnaround times have also become paramount, and these concerns are evolving, but are becoming more and more manageable as evidence continues to emerge with increasing payer reimbursement and development of technologies adept at facilitating the implementation of testing results [38].

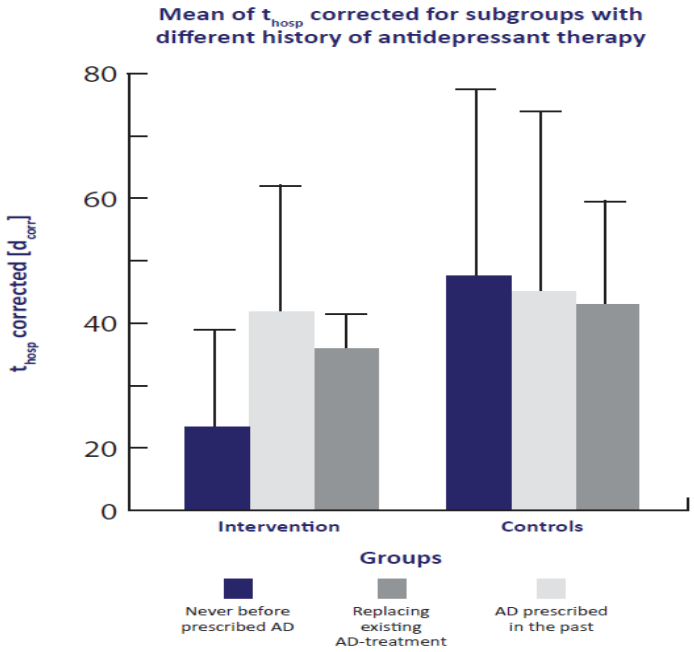

Figure 3. Mean lengths of hospital stays for cohorts with different antidepressant therapy histo-ries (adapted from Battig et al 2020).

Table 5. Description of intervention and control group (adapted from Battig et al 2020).

Parameter [unit]	Intervention (I), mean (SD)	Control (C), mean (SD)	*p*-Value	95%CI
Time spent in hospital (t_{hosp}) (uncorrected) [d]	54.1 d (21.8 d)	46.6 d (19.1 d)	0.035	0.55-14.56
Start of antidepressant therapy [d]	15.3 d (13.9 d)	8.1 d (11.3 d)	0.001	2.90-11.46
Time spent increasing dose of antidepressant [d]	17.7 d (14.5 d)	16.7 d (12.8 d)	0.694	-3.73-5.59
t_{hosp} corrected [d_{corr};d]	36.3 d_{corr} (19.3 d_{corr})	46.6 d (19.1 d)	0.003	-16.93 – -3.55
Waiting time for genotyping results [d]	17.8 d (13.6 d)	N/A	N/A	N/A
t_{hosp} AD-History 1 [d]	41.6 d (15.0 d)	50.2 d (22.5 d)	0.188	-21.69-4.46
t_{hosp} corrected AD-History 1 [d_{corr}]	24.7 $_{corr}$ (13.5 d_{corr})	50.2 d (22.5 d)	<0.001	-37.8 – -13.06
Difference in BDI-II[1] [points]	-17.1 p (11.9)	-15.1 p (9.8 p)	0.283	1.66 – -5.63
Improvement rate BDI-II[1] [points/d_{corr}]	-0.626 p/d_{corr} (0.762 p/d_{corr})	-0.38 p/d (0.33 p/d)	0.038	-0.015 – -0.472
Difference in GAF[2,3] [point]	17.3 p (11.9 d)	16.2 p (12.6 p)	0.684	6.31 – -4.16
Improvement rate GAF[2,3] [points/d_{corr}]	0.685 p/d_{corr} (0.946 p/d_{corr})	0.39 p/d (0.37 p/d)	0.079	0.623 – -0.036

[1]: Difference in BDI-II measured at admission and at disharge; [2]: Difference in GAF measured at admission and at discharge; [3]: The dataset of GAF was only complete in n= 37 in (I) and n = 54 in (C).

4. DISCUSSION

While there is much attention given to the application of PGx in psychiatry, considerable debate exists surrounding many developments in the field. For example, GWAS studying variation in patients treated with antipsychotic and antidepressant medications did not reveal clinically useful genetic markers. Additionally, early on, the Food and Drug Administration (FDA) did not find that clinical pharmacogenetic results from data yielded sufficient sensitivity and specificity for commercially available tests in psychiatry. PGx tests for psychiatry, rather, have received CLIA certification, however they do not possess sufficient predictive power for clinical use. Even tests that have been approved in an early phase of PGx testing in psychiatry, such as the Roche Diagnostics AmpliChip R CYP450 Test, which tests for 27 alleles in CYP2D6 and 3 alleles in CYP2C19b based on pharmacokinetic data and marketed for the antipsychotic drugs metabolized by CYP2D6 or CYP2C19, had modest clinical implementation. This may have been due to ambiguous interpretation of test results and lack of prospective data indicating clinical utility which led to issues with payer reimbursement for such an expensive diagnostic test [12].

Clinical trials considered under the scope of randomized studies for illuminating trial-and-error drugs may become limited by the approaches of precision medicine, as discussed here.

Additionally, even within precision medicine, some investigators are calling for pharmacogenomic testing to evolve beyond studying static DNA variation utilizing "combinatorial approaches" which combine static markers such as SNPs with epigenetic DNA alterations (methylation, histone acetylation) to enhance therapeutic drug monitoring considering the temporal variation of drug responses. [20] Menke et al propose utilizing machine learning to integrate sociodemographic data, and biomarkers from blood and epigenetic information to construct an algorithm that can predict clinical outcomes of medication. These algorithms are predicated on high specificity and sensitivity to maximize positive results. Such a scenario would proceed as follows: detecting variants such as CYP2D6 and CYP2C19 with existing ADTs with high plasma concentrations but low dosages or high dosages associated with low clinical response. Polygenic risk scores are then constructed through deep neural networks as a result of the machine learning algorithms to "decipher the genetic role in [medication] pharmacokinetics and pharmacodynamics." Thus, data on potential adverse drug reactions (ADRs) and clinical efficacy can then be elucidated; and variables predicting adverse effects and efficacy can be predicted.[20]

The availability, affordability and acceptability of testing along with the turnaround times have also become paramount, and these concerns are evolving, but are becoming more and more manageable as evidence continues to emerge with increasing payer reimbursement and development of technologies adept at facilitating the implementation of testing results [38].

As these, novel machine learning approaches for pharmacogenetic testing are being developed that could potentially transform discoveries in this area, these methods could form the basis for future studies for establishing the evidence basis for PGx testing in psychiatry. [39,40] Investigations in this field have focused on the combining extensive patient variables to elicit concise data on predicting clinical outcomes through novel PGx biomarker discovery. A major study was performed on MDD patients using machine learning methods that demonstrated medication response to antidepressants, and showed that statistically based machine learning studies found patterns in multivariable data such as demographic or clinical characteristics to predict therapeutic responses[41].

Another study revealed PGx biomarkers that lead to accurate prediction of 8-week treatment responses to citalopram and escitalopram including DEFB1, AHR, TSPAN5, and ERICH3 genes implicated in MDD disease risk and antidepressant response. [42] Ultimately, like other PGx initiatives, machine learning aims to translate population-level probabilities to individualized medicine to predict response for MDD patients. [42,43]

5. CONCLUSION

While pharmacogenetic testing in psychiatry is evolving, a semblance of clarity for providers and patients is underway. Drug-gene pairs with established clinical utility are being developed and agencies (e.g. CPIC, FDA) are issuing recommendations in their labeling of psychotropic medication. Polymorphisms are being continually discovered, enabling significant associations with drug response and adverse effects to be revealed. However, more studies are necessary to ensure the replicability of studies, including both retrospective and prospective trials, in order to provide a very strong evidence basis for clinical decision support tools enabling translation of genotype to phenotype correlation. Due to the robustness of clinical utility measurements of PGx drugs and the positive response of PGx-guided groups in medication evaluation studies for patients and their drug responses, it is recommended that psychiatrics utilize this data in the targeted treatment of mental health patents and mitigate adverse drug reactions.

Conflicts of Interest Statement

Author Priya Hays is employed by Hays Documentation Specialists, LLC. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Patents

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Appendix A

N/A

Appendix B

N/A

REFERENCES

1. Van Schaik RHN, Muller DJ, Serretti A, Ingelman-Sundberg M. Pharmacogenetics in Psychiatry: An Update on Clinical Usability. Front Pharmacology. 2020.
2. Lin E, Lin C-H Lin, Lane H-Y. Precision Psychiatry Applications with Pharmacogenomics: Artificial Intelligence and Machine Learning Approaches. Int J Mol Sci. 2020; 21(3):969
3. Gandal M.J., Leppa V., Won H., Parikshak N.N., Geschwind D.H. The road to precision psychiatry: Translating genetics into disease mechanisms. Nat. Neurosci. 2016;19:1397–1407. doi: 10.1038/nn.4409. - DOI - PubMed
4. Dalvie S., Koen N., McGregor N., O'Connell K., Warnich L., Ramesar R., Nievergelt C.M., Stein D.J. Toward a Global Roadmap for Precision Medicine in Psychiatry: Challenges and Opportunities. OMICS. 2016;20:557–564.-66
5. Williams L.M. Precision psychiatry: A neural circuit taxonomy for depression and anxiety. Lancet Psychiatry. 2016;3:472–480.
6. Battig VAD, Roll, SC, Hahn M. Pharmacogenetic Testing in Depressed Patients and Interdisciplinary Exchange between a Pharmacist and Psychiatrists Results in Reduced Hospitalization Times. Pharmacops -ychiatry. 2020;53:185-192.
7. Brown L, Eum S, Haga SB, Strawn JB, Zierhut JR. Clinical Utilization of Pharmacogenetics in Psychiatry-Perspectives of Pharmacists, Genetic Counselors, Implementation Science, Clinicians and Industry. Pharmacopsychiatry. 2020:53:162-173.
8. Sinyor M, Schaffer A, Levitt A. The sequenced treatment alternatives to relieve depression (STAR*D) trial: A review. Can J Psychiatry 2010;55:126-135.
9. Warden D, Rush AJ, Trivedi MH. The STAR*D Project results: A comprehensive review of findings. Curr Psychiatry Rep. 2007;9:449-459.
10. Bousman CA, Hopwood M. Commercial pharmacogenetic-based decision-support tools in psychiatry. Lancet Psychiatry. 2016;3:585-590.
11. Ramsey LB, Prows CA, Zhang K. et al. Implementation of pharmacogenetics at Cincinnati Children's Hospital Medical Center: Lessons Learned over 14 years of personalized medicine. Clin Pharmacol Ther. 2019;105:49-52.
12. Malhotra AK, Zhang J-P, Lencz T. Pharmacogenetics in psychiatry: translating research into clinical practice. Mol Psychiatry. 2012;17(8):760-769;
13. Bousman CA, Jaksa P, Pantelis C. Systematic evaluation of commercial pharmacogenetic testing in psychiatry: A focus on CYP2D6 and CYP2C19 allele coverage and results reporting. Pharmacogenet Genomics. 2017; 27:387-393.
14. Routhieaux M, Keels J, Tillery EE. The use of pharmacogenetic testing in patients with

schizophrenia or bipolar disorder: A systemic review. Ment Health Clin. 2019;8(6):294-302.
15. Thase ME, Nierenberg AA, Vrijland P, Van Oers, HJ, Schutte AJ et al. Remission With Mirtazapine and Selective Serotonin Reuptake Inhibitors: a Meta-Analysis of Individual Patient Data From 15 Controlled Trials of Acute Phase Treatment of Major Depression. Int. Clin. Psychopharmacol. 2010;25 (4), 189-198.
16. Ehret MJ. Central Nervous System. In Concepts in Pharmacogenomics. Ed. M Zdanowicz. 2017:283-308.
17. Yoshida K, Muller DJ. Pharmacogenetics of Antipsychotic Drug Treatment: Update and Clinical Implications. Mol Neuropsychiatry. 2019;5(suppl 1):1-26.
18. Jukic MM, Smith RL, Haslemo T, Molden E, Ingelman-Sundberg M. Effect of CYP2D6 Genotype on Exposure and Efficacy of Risperidone and Aripiprazole: a Retrospective, Cohort Study. Lancet Psychiatry. 2019;6 (5):418-426.
19. Rosenblat JD, Lee Y, and Mcintyre RS. Does Pharmacogenomic Testing Improve Clinical Outcomes for Major Depressive Disorder? A Systematic Review of Clinical Trials and Cost-Effectiveness Studies. J. Clin. Psychiatry. 2017;78 (6):720-729.
20. Menke A, Weber H, Deckert H. Roadmap for Routine Pharmacogenetic Testing in a Psychiatric University Hospital. Pharmacopsychiatry. 2020;53:179-184.
21. Hicks JK, Bishop JR, Gammal RS, Sangkuhl K, Bousman C, et al. A Call for Clear and Con-sistent Communications Regarding the Role of Pharmacogenetics in Antidepressant Pharmacotherapy. Clin Pharmacol Ther. 2020;107(1):50-52.
22. Solomon HV, Cates KW, Li KJ. Does Obtaining CYP2D6 and CYP2C19 Pharmacogenetic Testing Predict Antidepressant Response or Adverse Drug Reactions? Psychiatry Res. 2019;271:604-613.
23. De Donatis D, Florio V, Porcelli S, Saria A, Mercolini L, Serretti A., et al.. Duloxetine Plasma Level and Antidepressant Response. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2019;92:127-132.
24. Florio V, Porcelli S, Saria A, Serretti A, Conca A. Escitalopram Plasma Levels and Antidepressant Response. Eur. Neuropsychopharmacol. 2017;27(9):940-944.
25. Greden JF, Parikh SV, Rothschild AJ, Thase ME, Dunlop BW, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. Journal of Psychiatry Research. 201;111:59-67.
26. Bradley P, Shiekh M, Mehra V, Vrbicky K, Layle S, Olson MC, et al. Improved Efficacy With Targeted Pharmacogenetic-Guided Treatment of Patients With Depression and Anxiety: a Randomized Clinical Trial Demonstrating Clinical Utility. J. Psychiatr. Res. 2018;96:100-107.
27. Fabbri C, Tansey KE, Perlis RH, Hauser J, Henigsberg N, Maier W, et al. Effect of Cytochrome CYP2C19 Metabolizing Activity on Antidepressant Response and Side Effects: Meta-Analysis of Data From Genome-Wide Association Studies. Eur. Neuropsychopharmacol. 2018;28 (8):945-954.
28. Jukic MM, Haslemo T, Molden E, Ingelman-Sundberg M. Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: a Retrospective Study Based on 2,087 Patients. Am. J. Psychiatry.2018;175 (5):463-470.
29. Bousman CA, Arandjelovic K, Mancuso SG, Eyre HA. Pharmacogenetic tests and depressive-symptom remission: a meta-analysis of randomized controlled trials. Pharmacogenomics 2019;20(1):37-47.
30. Jukic, MM, Haslemo T, Molden E, Ingelman-Sundberg M. Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: a Retrospective Study Based on 2,087 Patients. Am. J. Psychiatry. 2018. 175 (5):463-470.

31. Hall-Flavin DK, Winner JG, Allen JD, Carhart JM, Proctor B, Snyder, KA, et al. Utility of Inte-grated Pharmacogenomic Testing to Support the Treatment of Major Depressive Disorder in a Psychiatric Outpatient Setting. Pharmacogenet. Genomics 2013;23(10):535-548.
32. Perez V, Salavert A, Espadaler J, Tuson M, Saiz-Ruiz J, Saez-Navarro C.,et al. Efficacy of Prospective Pharmacogenetic Testing in the Treatment of Major Depressive Disorder: Results of a Randomized, Double-Blind Clinical Trial. BMC Psychiatry. 2017;17 (1):250.
33. Leckband SG, Kelsoe JR, Dunnenberger HM, George AL, Tran E, Berger R, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype and Carbamazepine Dosing. Clin. Pharmacol. Ther. 2013;94 (3):324-328.
34. Hou L, HeilBronner U, Degenhardt F, Adli M, Akiyama K et al. Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. Lancet. 2016;387(10023):1085-1093.
35. International Consortium on Lithium Genetics. Association of Polygenic Score for Schizo-phrenia and HLA Antigen and Inflammation Genes With Response to Lithium in Bipolar Affective Disorder: A Genome-Wide Association Study. JA-MA Psychiatry. 2018;75(1):65-74.
36. Fan M, Bousman CA. Commercial Pharmacogenetic Tests in Psychiatry: Do they Facilitate the implementation of Pharmacogenetic Dosing Guidelines. Pharmacopsychiatry. 2020;53:174-178.
37. Bousman CA, Dunlop BW. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. The Pharmacogenomics Journal. 2018;18:613-622.
38. Bousman CA, Bengesser SA, Aitchison KJ, Amare AT, Aschauer H et al. Review and Consensus on Pharmacogenetic Testing in Psychiatry. Pharmacopsychiatry. 2021l54:5-17.
39. Athreya AP, Iyer R, Wang L, Weinshilboum RM, Bobo WV. Integration of machine learning and pharmacogenomic biomarkers for predicting response to antidepressant treatment: can computational intelligence be used to augment clini-cal assessments? Pharmacogenomics. 20(14) Editorial.
40. Dwyer DB , Falkai P , Koutsouleris N . Machine learning approaches for clinical psychology and psychiatry. Annu. Rev. Psychol. 14, 91–118 (2018).
41. Iniesta R , Stahl D , McGuffin P . Machine learning, statistical learning and the future of biological research in psychiatry. Psychol. Med. 46(12), 2455–2465 (2016).
42. Neavin D , Carrillo-Roa T et al. Pharmacogenomics-driven prediction of antidepressant treatment outcomes: a machine-learning approach with multi-trial replication. Clin. Pharmacol. Ther. 106(4), 855–865 (2019).
43. Gupta M , Neavin D , Biernacka J et al. TSPAN5, ERICH3 and selective serotonin reuptake inhibitors in major depressive disorder: pharmacometabolomics-informed pharmacogenomics. Mol. Psychiatry 21(12), 1717–1725 (2016).

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