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Pharmacogenomic Testing in Depression Treatment Decision Making: Clinical Pearls for Everyday Practice

Based on a Medscape Education Online Activity

CME INFORMATION

CME/ABIM MOC/CE

Release Date: 04/17/24
Expiration Date: 04/17/25

TARGET AUDIENCE

This activity is intended for primary care physicians, psychiatrists, nurse practitioners, physician assistants, nurses/advanced practice nurses, pharmacists, and other clinicians who treat patients with major depressive disorder (MDD).

GOAL STATEMENT

The goal of this activity is for learners to be better able to examine the scientific rationale for pharmacogenetic (PGx) testing in depression medication selection, translate the latest clinical evidence for PGx testing, and incorporate PGx testing into the clinical management of patients with MDD.

LEARNING OBJECTIVES

Upon completion of this activity, participants will:

Have increased knowledge regarding the

- Scientific rationale for PGx testing in depression care

Have greater competence related to

- Identifying patients with MDD who may benefit from PGx testing and utilizing PGx test results as a clinical guidance tool in medication selection for patients with MDD

Demonstrate greater confidence in their ability to

- Translate available clinical data for and communicate with patients regarding PGx testing

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Pharmacogenomic Testing in Depression Treatment Decision Making: Clinical Pearls for Everyday Practice

Jeffrey R. Bishop, PharmD, MS, BCPP, FCCP

MAJOR DEPRESSIVE DISORDER AND THE DEFINITION OF TREATMENT RESPONSE

Major depressive disorder (MDD) is a chronic mental illness associated with significant disability, morbidity, and mortality in some patients that results in substantial social and economic consequences when not effectively treated.[1] The use of antidepressant therapies to treat MDD are considered first-line treatment options in established treatment guidelines and by international experts.[2,3] However, according to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, approximately 30% to 50% of patients will not respond to initial antidepressant therapy, either due to treatment ineffectiveness or drug-induced adverse events.[1,4] Further, the results of the STAR*D trial also show that rates of adverse events increase with each subsequent antidepressant trial.[5] For patients with MDD, the goal of treatment is remission, with a return to full functioning in all areas of life.[6,7] Efficiently optimizing the selection and dosing of antidepressant therapies is essential to achieve this goal.

While there are opportunities for symptom improvement after switching medications, effectiveness research also demonstrates that rates of remission (defined as absent or minimal symptoms defined either clinically or by rating scales) and rates of response (defined as ≥ 50% reduction in symptom rating scores) continue to decrease with each subsequent medication trial, leading to further challenges for clinicians in helping patients manage their depression.[8] Although a 50% reduction in depression symptoms may be indicative of a treatment response, it is important to note that a severely depressed patient may show a 50% improvement on a depression rating scale, but still be experiencing debilitating depression and hampered range of function.[6] Multiple medication trials can prolong the time to remission, increasing the patient burden and risk for severe outcomes, such as disability and suicide.[9]

An inadequate response to treatment may be impacted by several factors, including[6,7]:

- Adherence to treatment
- Dosing
- Length of the medication trial
- Impact of comorbidities or drug interactions
- Tolerability and safety
- Genetic factors that impact tolerability, safety, and efficacy of treatment

THE ROLE OF GENETICS IN PHARMACOKINETICS AND PHARMACODYNAMICS

The importance of genetics is becoming increasingly clear in depression management; genetic factors may contribute significantly to treatment outcomes.[10] Genetic variations, such as single-nucleotide polymorphisms (SNPs), insertion/deletion of specific sequences, and copy number variations (CNVs) (eg, whole or partial gene duplications or deletions), can have an impact on drug pharmacokinetics (PK; eg, absorption, distribution, metabolism, and elimination) and pharmacodynamics (PD; eg, the pharmacologic effects of treatment).[11] Extensive research accrued over many years has identified and characterized genetic variants that can influence the PK and PD of specific drug therapies including antidepressants. The importance of these factors may vary depending on drug, drug metabolism genetics (**TABLE 1**),[12] and clinical outcome. Some may impact dosing approaches, while others may warrant the consideration of alternative therapies. Other variants may result in severe, or even life-threatening, adverse reactions in individuals who are exposed to certain treatments.[11]

Most of the currently available antidepressant treatments undergo hepatic metabolism. Several genes encoding oxidative and conjugative metabolizing enzymes contain variants driving enzymatic activity.[11,13,14] Genetic variations in drug transporters may impact drug distribution in the liver, gut, and at the blood-brain barrier,

Table 1. Genetics Definitions[11,12]

Term	Explanation
Genotype	Genetic make-up of an individual at a given location in the genome
Phenotype	Functional outcome or an individual's observable traits resulting from genotype(s)
Haplotype	A set of genetic determinants located on a single chromosome that tend to be inherited together
Diplotype	Two alleles inherited by an individual for a particular gene
Star (*) Nomenclature	*1 = the reference sequence, usually the first described sequence Additional stars (*) represent genetically distinct alleles, usually haplotypes or single-nucleotide polymorphisms
Pharmacogenetics and Pharmacogenomics	Collectively these terms refer to the study of how genetic variation may impact drug treatment outcomes Pharmacogenetics often refers to individual genes or specific genetic variants and pharmacogenomics refers to multiple genes and variants across the genome

Table 2. Genes Encoding for Antidepressant Metabolizing Enzymes[15-17]

Gene	Description
CYP2D6	Mapped to chromosome 22q13 with numerous variants and haplotypes identified; these alleles have been studied extensively in several population types Alleles can be categorized into activity scores; diplotypes may be translated into poor, intermediate, normal, and ultrarapid metabolizer groups This gene is especially prone to structural variations, such as gene deletion, multiplication, and rearrangement with *CYP2D7*
CYP2C19	Mapped to chromosome 10q23.33 with numerous variants and haplotypes identified Allele frequency differs greatly across diverse populations with diplotypes translated into poor, intermediate, normal, rapid, and ultrarapid metabolizer groups
CYP2B6	Mapped to chromosome 19q13.2 with more than numerous haplotypes identified across several population types with diplotypes translated into poor, intermediate, normal, rapid, and ultrarapid metabolizer groups

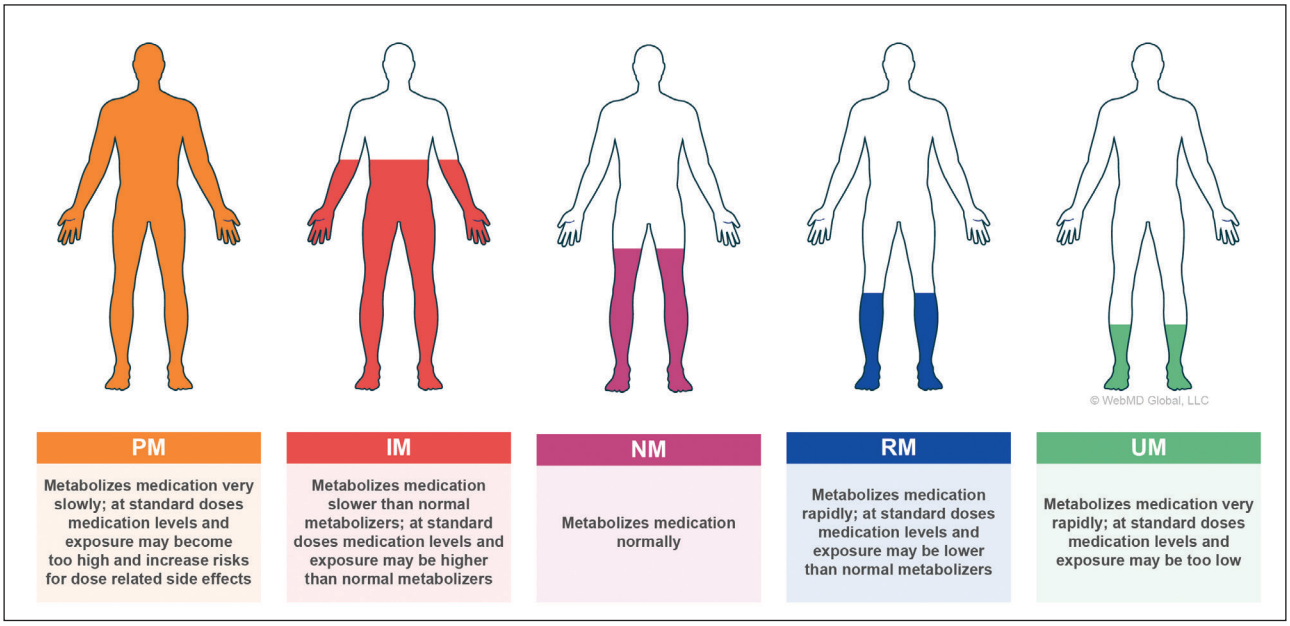
which may in turn alter the drug's PK profile.[14] Variations in genes that encode for neurotransmitter receptors and reuptake transporters, including genes for signal transduction, gene transcription, and protein folding and trafficking, may have a significant impact on a drug's pharmacodynamic qualities (**TABLE 2**).[14-17]

Genes encoding drug metabolizing enzymes with well-defined genetic variations important for commonly used antidepressants (eg, CYP2D6, CYP2C19, and CYP2B6) and SNP combinations may result in 5 genetically estimated metabolizer categories[18-21]:

- Poor: a complete absence of enzymatic activity
- Intermediate: a reduction of enzymatic activity compared to normal metabolizers
- Normal: unaffected or minimally effected enzymatic activity; historically also referred to as "extensive metabolizers"
- Rapid: an increase in enzymatic activity compared to normal metabolizers (this category is relevant to CYP2C19 and CYP2B6)
- Ultrarapid: a substantial increase in enzyme activity compared to normal metabolizers

Other drug metabolizing enzymes, such as CYP1A2 and CYP3A4, are also important for the metabolism of commonly used antidepressants. Like CYP2D6, CYP2C19, and *CYP2B6*, they also contain genetic variations that may impact metabolism, and in the case of CYP1A2, the extent to which enzyme induction may occur in the context of environmental exposures (eg, smoking). The impacts of genetic variation in these additional genes related to antidepressants and other medications is a growing area of research. For antidepressants with an active parent compound and minimally active metabolite, the same dose

Figure. Effect of *CYP2C19* Genotype on Escitalopram Serum Concentration[22]*



IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer. *Assumes active parent drug, impacts on prodrug compounds may be different.

administered to persons of differing genetic metabolic predisposition may result in substantially different exposures (**FIGURE**).[22,23]

Pharmacodynamic genes can also impact antidepressant outcomes, through the alteration of target receptors, transporters, or other genes involved with neurotransmitter disposition.[18] Two genes that have been extensively studied and that are included on some clinically available pharmacogenomic test panels include the serotonin transporter (*SLC6A4*) and the serotonin-2A receptor (*HTR2A*) genes. Like the aforementioned drug metabolizing enzyme genes, *SLC6A4* and *HTR2A* also contain numerous genetic variants, some of which may impact expression or function and associations with treatment outcomes.[24-26]

Unlike the drug metabolism genes, there is not yet broad consensus on the translation of genotype to phenotype groups and the nomenclature that might be most applicable to pharmacogenomics. The gene variants that are most widely studied and included on some clinically available pharmacogenomic tests include the 5HTTLPR (serotonin transporter linked polymorphic region) that resides in the promoter region of *SLC6A4* and impacts 5HTT expression, and *HTR2A*, in which 2 variants in the promoter region (rs6311 and rs6313) may impact 5HT2A expression.[24-26] Current estimates show that, when genotyped with a panel of pharmacogenes, roughly 90% of individuals may have at least 1 genetic variant that may prompt changes in dosing or medication. However, the presence of a genetic variant does not always warrant such action and depends on the use of an interacting medication, as well as other clinical contextual factors.[27] Therefore, it is important to define an individual's genetic profile and examine how the results might influence treatment and dose choice and treatment response, a practice known as pharmacogenomics.[9] The rationale for pharmacogenomic testing rests upon several factors. For example, knowing the patient's genotype can help clinicians identify genetic factors that may impact dosing strategies, treatment response, and tolerability.[21] However, a common misconception is that pharmacogenomic testing is the only factor that should be considered for patients who have not responded to multiple antidepressant therapies. Though pharmacogenomics is a useful tool, it is only one part of a complex puzzle that can help clinicians with treatment selection and should not be used as a primary source for treatment choices.[9,21]

PHARMACOGENOMICS AND UNMET NEEDS IN PATIENTS WITH DEPRESSION

Currently, 4-week to 6-week antidepressant trials are necessary to evaluate treatment effectiveness trajectories in patients with MDD. The combination of time to evaluate effectiveness, tolerability challenges, and the logistic fac-

tors related to appointment scheduling, combined with the common "trial-and-error" approach to selecting antidepressants can lead to lengthy, frustrating, and expensive journeys for patients seeking relief.[9,21,28] Pharmacogenomics testing can aid clinicians and patients with drug selection and dosing decisions and can help evaluate how an individual's genomic profile can influence their response to treatment.[9,27] The use of pharmacogenomics can help improve patient care by helping clinicians and patients optimize treatment choices and dosages (though should not be used as the only source for treatment choices), decreasing the risk of adverse events, and increasing satisfaction via personalized treatment selection.[27]

Pharmacogenomic testing to guide antidepressant use has not yet been widely adopted as standard of practice in routine clinical care, and its use may differ based on location and clinical practice environment. Currently, published data from randomized controlled clinical trials using pharmacogenomics specifically to guide depression treatments are slowly accumulating through a combination of published and in-progress industry and government-funded studies.[10,29,30] A meta-analysis of currently published studies reflect a substantial impact of pharmacogenomics on achieving remission status in patients with depression.[30]

The GUIDED trial was a randomized clinical trial that examined the utility of pharmacogenomic testing in mental health conditions.[7,31,32] The trial included 1167 outpatients diagnosed with MDD and with an inadequate response to at least 1 antidepressant.[31] Although this study did not meet its primary endpoint, the results of the secondary outcomes showed that pharmacogenomic-guided treatment resulted in greater improvements in treatment response (26.0% vs 19.9%, $P = .013$) and remission (15.3% vs 10.1%, $P = .007$) after 8 weeks of treatment, compared with treatment as usual (TAU).[31]

The PRIME study was a randomized clinical trial that included 1541 patients with MDD that compared pharmacogenomic-guided treatment with TAU. The results showed that the pharmacogenomic-guided group was more likely to receive a medication with a lower potential for drug/drug interactions. Further, patients had higher remission rates during the 24-week study period, but these differences were no longer significant, compared to TAU, at the 24-week point.[23]

The PREPARE study was a prospective evaluation of 6994 patients who received either pharmacogenomic-guided care or TAU with follow up over the course of 12 weeks. The goal of this study was to evaluate the impact of a 12-gene pharmacogenomic panel on clinically relevant adverse drug reactions. Participants were randomized to pharmacogenomic guidance vs usual care. Medications across different therapeutic areas were assessed in relation to pharmacogenomic information and included both antidepressant and antipsychotic medications. Overall, the use of pharmacogenomic information reduced adverse drug reactions in all treatment classes by 30%.[33]

In another recently published study focusing on tricyclic antidepressants (TCAs), 111 participants were randomized to receive pharmacogenomics-informed treatment vs usual care and followed up over the course of 7 weeks. The primary outcome was time to attain therapeutic blood levels of the TCA. Pharmacogenomics-informed care resulted in a shorter time to therapeutic concentrations and better tolerability, but no significant differences in change in depression symptoms between groups.[30]

Other antidepressant-focused pharmacogenomic trials underway include the PRESIDE[10] and ADOPT PGx studies, which will provide further assessments of the benefits of using pharmacogenomics to help guide treatment in patients with MDD.

Overall, studies to date present data suggesting potential benefits of pharmacogenomic testing on elements of symptom improvement and tolerability. Additional research is needed to clarify at what point in treatment testing may be most beneficial and if there are specific patient characteristics that may help determine who may benefit most from testing. Despite these knowledge gaps, in a survey of 168 psychiatrists and general practitioners who had experience with pharmacogenomic testing, 80% of respondents were satisfied or very satisfied with the testing outcomes, and more than 75% reported satisfactory or higher than satisfactory comprehension of test results.[21,34]

GUIDELINE RECOMMENDATIONS FOR USING PHARMACOGENOMICS TO INFORM ANTIDEPRESSANT SELECTION AND DOSING

Recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) contain guidance regarding how to consider the use of existing genetic information to guide antidepressant selection and dosing.[18,35,36]

For example, the CPIC guidelines for *CYP2C19* poor metabolizers recommend choosing an alternative therapy or a 50% reduction in the starting doses, and slower titration schedule, of the selective serotonin reuptake inhibi-

tors (SSRIs) citalopram, escitalopram, and sertraline, and for tertiary amine tricyclic antidepressants, such as amitriptyline. The recommendations for rapid and ultrarapid metabolizers suggest choosing a therapy of a different class of antidepressant, as these patients may be less likely to respond to treatment with an SSRI or tricyclic therapy.[35-37]

For *CYP2D6* poor metabolizers, CPIC recommends up to a 50% reduction in the initial dose and lower maintenance doses of most tricyclic antidepressants, fluvoxamine, paroxetine, and vortioxetine, and suggests using an alternate antidepressant treatment for venlafaxine.[18,37] Alternate antidepressant therapies that are not metabolized by *CYP2D6* are also recommended for ultrarapid metabolizers when considering the use of paroxetine or vortioxetine.[18]

For *CYP2B6* poor metabolizers, CPIC recommends a lower starting dose, slower titration rate, and 25% reduction of the standard maintenance dose for sertraline treatment. Therapy initiation with the recommended starting dose of sertraline is recommended for rapid and ultrarapid metabolizers.[18] As a result of accumulating data on the combined importance of CYP2C19 and CYP2B6, latest CPIC guideline also proposes guidance to sertraline dosing based on the combination of genotypes for these 2 genes.

Pharmacogenomics language in the U.S. Food and Drug Administration (FDA) product labeling is evolving to become more informative for dosing guidance. FDA curated tables, including the FDA Table of Pharmacogenomic Associations[38] and the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling,[39] are evolving resources to identify how and where pharmacogenomic-related information is included in drug labeling. Historically, pharmacogenomic information included in drug labeling was based on information submitted by sponsors as part of new drug approvals or indications. Thus, the specificity of the language varies across medications and may not include data generated outside of the drug approval process.

Lastly, commercial and clinical laboratories that provide pharmacogenomic testing will often provide recommendations with the return of results. There is currently no gold standard for this process, and approaches differ across labs. Therefore, when using a clinical test to inform antidepressant use, it is important to gain familiarity with the test (eg, what genes and variants are tested) and the results (eg, how and why results are returned in specific formats along with the evidence used to inform those interpretations).[9]

THE IMPACT OF DRUG INTERACTIONS AND PHENOCONVERSION

Phenoconversion is a phenomenon that occurs when an individual's genotype-based phenotype prediction for drug metabolism (eg, normal metabolizer) does not correlate with the individual's true metabolic capacity at a specific point in time due to the contributions of non-genetic factors.[20] For example, strong CYP2D6 inhibitors can convert CYP2D6 normal or intermediate metabolizers into phenotypically poor or intermediate metabolizers. Phenoconversion can result from drug/drug interactions, which in the context of known genetic information is also known as drug-drug-gene interactions.[20]

COMMUNICATING WITH PATIENTS ABOUT PHARMACOGENOMIC TESTING

The relative novelty of pharmacogenomic testing, and the potential impact it has on patient outcomes, underscores the importance of proper communication with patients to help them interpret test results and understand what information pharmacogenomic testing may or may not provide. A common misconception among patients, and sometimes among clinicians, is that the test results will provide the single best treatment for the patient, when in reality pharmacogenomic testing may provide additional biologic information about the patient that may aid in treatment and dose selection in the context of the patient's unique clinical situation.[9] It is, therefore, important to communicate with the patient, prior to testing, that genetic factors are just one component in the larger constellation of considerations that contribute to the treatment selection process, and that test results can either help rule in or rule out the possibility of genetic variations associated with medication selection and dosing.[9]

After the test is performed and the results are available, it is important that clinicians reiterate the points made during the pretest discussion and discuss actions that might maximize the benefits of the test results. Since the report may be lengthy and contain terminology that the patient may find unfamiliar and overwhelming, clinicians may also want to review the report together with the patient, to explain how the results are organized and what they mean. Importantly, patients should be encouraged to refrain from making any treatment changing decisions on their own before discussing the results and the implications of the test results with their clinician.[9] Depending on the clinic environment and time available for discussions with patients, an interprofessional collaborative approach to counseling and education may be beneficial.[40] Specifi-

cally, a growing number of board-certified ambulatory care and psychiatric pharmacists are positioned to integrate pharmacogenomic results interpretation into medication therapy management (MTM) or comprehensive medication management (CMM) visits with patients.[9] Patients who understand the results of their pharmacogenomic testing may feel more comfortable sharing the results with their other clinicians in order to optimize their care and health decisions going forward.[41] There is a growing appreciation of how pharmacogenomic information can enhance the overall patient experience with healthcare.[42]

INTEGRATING PHARMACOGENOMICS INTO CLINICAL CARE: CASES FOR CONSIDERING THE USE OF PHARMACOGENOMICS IN AN ELDERLY PATIENT

In a recent published case study, an elderly patient aged 79 years presented with severe depression with psychotic symptoms and anxiety. She was physically healthy and was not taking any medications. Between June 2020 and June 2021, she received treatment with several antidepressants and mood stabilizers, including escitalopram, mirtazapine, sertraline, venlafaxine, olanzapine, risperidone, lorazepam, aripiprazole, brexpiprazole, and amisulpride, over the course of 6 treatment attempts. She experienced several extrapyramidal effects and other adverse events during treatment, with no improvements in her depression or psychotic symptoms, which sometimes worsened. During the sixth attempt, the patient received pharmacogenomic testing, which revealed rapid metabolizer status for *CYP2B6* and *CYP2C19*, and normal metabolizer status for *CYP2D6*. Based on the patient's treatment history, depression characteristics, and the results of the pharmacogenomic testing, the patient then initiated treatment with quetiapine, the TCA maprotiline, and pregabalin for anxiety, after which she experienced significant improvements in her depression, with no further psychotic episodes.[43]

This particular case is remarkable in the fact that the patient was not receiving treatment for any medical comorbidities at the time of presentation. In fact, treatment choices for elderly patients must include considerations of the impact of other types of therapies that may introduce potential safety risks. As noted earlier, laboratories differ in how they return pharmacogenomic test results. Some focus specifically on mental health medications and others provide information for other classes of drugs. In situations where results are focused only on mental health treatments, several resources are available to help clinicians understand the implications of pharmacogenomic test results for other medications to mitigate potential risks, including:

- The CPIC website tool for possible drug/drug interactions[44]
- The FDA Table of Pharmacogenomic Biomarkers in Drug Labeling[39]
- The FDA Table of Pharmacogenetic Associations[40]
- The Pharmacogenomics Knowledgebase (PharmGKB) tool with genotype results for any test, which will display FDA, CPIC, and DPWG treatment recommendations, if available[45]
- Sequence2Script tool to enter genotype results from any test to display FDA, CPIC, and DPWG treatment recommendations, if available. Also contains an option to integrate current medications to assess phenoconversion[46]

USE OF PHARMACOGENOMICS IN AN ADULT FEMALE PATIENT

A 35-year-old woman presented at a clinical practice with chronic MDD; she had no family history of depression and had not reported any substance abuse. She had undergone 3 treatment attempts with the SSRIs sertraline, paroxetine, and fluoxetine, all of which had minimal to no effect. She experienced several side effects while receiving treatment, including sexual dysfunction, fatigue, and weight gain. Pharmacogenomic testing revealed that she has 2 "short" alleles of the gene SLC6A4. In this patient's case, the presence of the "short" alleles may impact her body's ability to metabolize SSRI medications, which may indicate that treatment with an antidepressant from a different treatment class may be more effective.[18]

USE OF PHARMACOGENOMICS IN CHILDREN AND ADOLESCENTS

A 17-year-old boy with chronic MDD presented with his parents at a clinical practice. He had not responded to 3 previous antidepressant treatments, or had a partial response to treatment, and had experienced intolerable side effects. His MDD was impacting his performance at school, and he had trouble in his home and social relationships. His parents were also distressed, as they were concerned about their son's well-being and safety. The clinician discussed the possibility of performing pharmacogenomic testing with the patient and his family and explained what the test may or may not reveal, and how the results could possibly be used, together with information regarding the patient's history and his

preferences, to help inform the next treatment choice and dose.

The American Academy of Child and Adolescent Psychiatry (AACAP) does not currently recommend that pharmacogenomic testing be used when considering treatment choices for children and adolescent patients.[47] However, though more evidence is needed regarding the use of pharmacogenomics testing in this population, testing may help inform dosing for antidepressants commonly used in child and adolescent psychiatry, as well as the tolerability of some psychotropic medications.[48,49]

CONCLUSIONS

The use of pharmacogenomic testing, paired with clinical practice guidelines and evidence-based patient care, can help clinicians optimize antidepressant treatment and doses for patients with MDD. Clinicians should help patients set realistic expectations of testing and communicate the results of pharmacogenomic testing in a clear, concise manner. Patients and clinicians should understand that pharmacogenomic testing should not be expected to reveal one "best" treatment option, but rather understand how genetics can impact treatment selection, and how the test results help inform evidence-based, guideline-driven care, ultimately resulting in improved outcomes for patients with MDD.[9] ●

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