Therapeutic Perspective

CLINICAL INVESTIGATION

Pharmacogenomic testing to guide treatment using antipsychotic medications

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This review evaluates the utilization of pharmacogenomic testing to guide treatment with antipsychotic medications as well as the evidence supporting the use of pharmacogenomic testing. There are two basic objectives for using pharmacogenomic testing. The first pharmacogenomic objective is to minimize adverse effects. The second pharmacogenomic objective is to improve clinical outcomes. While available pharmacogenomic testing has been demonstrated to increase the likelihood of achieving a good response, the primary current indication is to improve patient safety.

Keywords: akathisia • allele • haplotype • reference sequence number • tardive dyskinesia • variable nucleotide tandem repeat • VNTR

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The use of pharmacogenomic testing to decrease the likelihood of the adverse events associated with the use of antipsychotic medications involves determining the variations in genes that influence the pharmacokinetics of an antipsychotic drug, as well as the genes that influence the pharmacodynamic responses of patients to these medications [1]. Pharmacokinetic studies of antipsychotic medications have provided a body of evidence that is used to predict the probable serum levels of these medications based on testing of the genes that influence the metabolism of each specific antipsychotic medication.

Patients with impaired metabolic capacity are at greater risk of experiencing adverse outcomes if their physicians assume that their metabolic capacity is normal. In addition, variations in the genes that code for transporters of neurotransmitters, as well as genes that code for neurotransmitter receptors that influence the response to a psychotropic medication, can identify patients who are at increased risk for adverse events even though they have adequate metabolic capacity.

Research designed to improve pharmacogenomic predictions of the probability of a patient to safely respond to an antipsychotic medication has increased dramatically over the past decade. However, the integration of the high volume of emerging pharmacogenomic research findings has proven to be challenging. It is also true that the translation of systematic scientific reviews must overcome significant barriers [2]. This review identifies eleven genes that were selected for inclusion in this review because they are currently being genotyped to guide the treatment of patients taking antipsychotic medications. These eleven genes are *CYP2D6*, *CYP2C19*, *CYP1A2*, *COMT*, *SLC6A2*, *HTR1A*, *HTR2A*, *HTR2C*, *DRD2*, *DRD3* and *DRD4*.

Given the expanding research evidence base, it is inevitable that additional relevant genes will be included in future clinical pharmacogenomic applications. The literature review for this report was compiled through an ongoing surveillance of the scientific papers which report associations between gene variants and antipsychotic efficacy or side effects. In the future, the identification of additional variations within clinically relevant genes is anticipated to lead to increasingly accurate predictions. Clinical psychiatric pharmacogenomic testing has been available for the past 8 years from major reference laboratories. During this time,

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Table 1. Pharmacogenomically relevant drug metabolizing enzyme genes for atypical antipsychotic drugs.

Generic name	Primary metabolic pathway	Secondary metabolic pathways
Clozapine	*CYP1A2*	*CYP3A4, CYP2C19*
Risperidone	*CYP2D6*	*CYP3A4*
Olanzapine	*CYP1A2*	*CYP2D6*
Quetiapine	*CYP3A4*	*CYP2D6*
Ziprasidone	*CYP3A4*	*CYP2D6*
Aripiprazole	*CYP3A4*	*CYP2D6*
Iloperidone	*CYP2D6*	*CYP3A4, CYP1A2*

the 'value- added' benefit of pharmacogenomic testing has increased on an annual basis. It is expected that the rate of improved prediction will increase dramatically over the next decade.

Informative genes

■ *CYP2D6*

CYP2D6 is located on the long arm of chromosome 22 (e.g., 22q13.1) and codes for the 2D6 enzyme. Risperidone is primarily metabolized by the 2D6 enzyme (Table 1) [3].

Traditionally, four metabolic phenotypes have been derived from genotyping *CYP2D6*. The most important phenotype is the 'poor metabolizer' who lacks an active copy of *CYP2D6*. The current most widely accepted definition of an intermediate metabolizer phenotype is a genotype with only one active allele. An extensive or normal metabolizer most commonly refers to a patient with two active copies of the gene. The ultra-rapid metabolizer phenotype is defined as having more than two active copies of the gene, or two or more enhanced activity alleles.

Individuals who are poor *CYP2D6* metabolizers have been shown to have an increased frequency of side effects when taking standard doses of risperidone [4]. Poor *CYP2D6* metabolizers have also had an increased probability of developing hyperprolactinemia [5]. Furthermore, individuals who are ultra-rapid metabolizers of *2D6* substrate medications are unlikely to achieve adequate serum levels when taking standard doses of risperidone.

Aripiprazole is substantially metabolized by the 2D6 enzyme, but it is also metabolized by the 3A4 enzyme (Table 1). Consequently, it is usually possible for patients with decreased *CYP2D6* metabolic capacity to tolerate aripiprazole at reduced doses if their *CYP3A4* metabolic capacity is adequate.

Four of the typical antipsychotic medications are primarily metabolized by the 2D6 enzyme (Table 2). Chlorpromazine and thioridazine are quite sedating and chronic use has been associated with tardive dyskinesia. Haloperidol is a typical antipsychotic medication that is primarily a *2D6* substrate and has a relatively high occurrence of extrapyramidal side effects. Perphenazine is yet another typical antipsychotic medication that is primarily a *2D6* substrate and is poorly metabolized by the other cytochrome P450 enzymes. Perphenazine has comparable efficacy to the most widely used atypical antipsychotics, although it does have a moderately greater risk of extrapyramidal side effects [6]. Additional research is needed to further clarify the mechanisms by which *CYP2D6* genotypic variations can be used to predict the development of specific adverse effects. However, increased serum levels of the antipsychotic medications and their specific metabolites are presumed to contribute to the greater likelihood of side effects.

■ *CYP2C19*

CYP2C19 is located on the long arm of chromosome 10 (e.g., 10q24.1-q24.3). The 2C19 enzyme plays a limited role in the metabolism of most antipsychotic medications.

Table 2. Pharmacogenomically relevant drug metabolizing enzyme genes for typical antipsychotic drugs.

Generic name	Primary metabolic pathway	Secondary metabolic pathways
Chlorpromazine	*CYP2D6*	*CYP1A2*
Thioridazine	*CYP2D6*	*CYP1A2, CYP2C19*
Perphenazine	*CYP2D6*	No secondary pathway
Haloperidol	*CYP2D6*	*CYP3A4, CYP1A2*

However, the 2C19 enzyme is involved in the metabolism of clozapine and thioridazine (Tables 1 & 2).

CYP1A2

CYP1A2 is located on the long arm of chromosome 15 (e.g., 15q24). Clozapine and olanzapine are primarily metabolized by the CYP1A2 enzyme (Table 1). However, chlorpromazine, thioridazine and haloperidol can be metabolized by *CYP1A2* if their primary metabolic capacity is inadequate (Table 2). While *CYP1A2* is primarily responsible for clozapine metabolism, four other cytochrome P450 enzymes are also involved in the metabolism of clozapine [7].

COMT

COMT is located on the long arm of chromosome 22 (e.g., 22q11.21). The COMT enzyme inactivates catechol neurotransmitters by methylation. *COMT* variation has been reported to influence the response of patients to treatment with antipsychotic medications [8]. Hospitalized schizophrenic patients can be classified as having either low *COMT* activity or high *COMT* activity based on the two alleles that code for either valine or methionine at amino acid location number 158 (e.g., 158 Val/Met or rs4860) [9]. Patients with higher activity based on having either one or two of the higher activity valine alleles have been reported to be more likely to respond to typical antipsychotic medications than patients who are homozygous for the lower activity methionine allele.

In contrast, an atypical antipsychotic medication, olanzapine, has been reported to have a better response in patients who are homozygous for the lower activity Met allele [10]. Additional research is needed to further clarify the influence of *COMT* activity in response to antipsychotic medications.

SLC6A2

SLC6A2 is located on the long arm of chromosome 16 (e.g., 16q12.2). Variations of *SLC6A2* in patients with schizophrenia have been associated with different responses to both risperidone and olanzapine [11]. Patients with one or two thymine alleles of the 182T/C single nucleotide polymorphism (SNP) (i.e., rs2242446) have had greater improvement of their positive symptoms than patients who were homozygous for the cytosine allele. Those patients who were homozygous for the adenine allele of the 1287G/A SNP (i.e., rs5569) also had greater improvement of their positive symptoms than did patients who had one or two guanine alleles.

HTR1A

HTR1A is located on the long arm of chromosome 5 (e.g., 5q11.2–q13). Ziprasidone [12] and aripiprazole [13] have a relatively strong affinity to the *HTR1A* receptor. It has been reported that patients with the cytosine allele of the 1019C/G SNP (i.e., rs6295) have a better response to ziprasidone and aripiprazole. The cytosine allele has also been reported to predict a greater improvement in negative symptoms for risperidone and olanzapine [14].

HTR2A

HTR2A is located on the long arm of chromosome 13 (e.g., 13q14-q21). The adenine allele of the 1438G/A SNP (i.e., rs6311) and the thymine allele of the 102T/C SNP (i.e., rs6313) have been associated with a better response to clozapine than the guanine allele of rs6311 or the cytosine allele of rs6313 [15]. Another variant of *HTR2A*, 1354C/T (i.e., rs6314), has also been associated with clozapine response. Patients who had one or more copies of the cytosine allele have been reported to have a better response to clozapine than patients who were homozygous for the thymine allele of rs6314 [16].

Patients treated with risperidone for schizophrenia, who were homozygous for the cytosine allele of 102T/C (i.e., rs6313), had more improvement in their negative symptoms than did those who carried one or more copies of the thymine allele in a Chinese sample [17]. A similar association with the adenine allele of 1438G/A (i.e., rs6311) was reported in patients in a French sample who were treated with risperidone and other atypical antipsychotic medications [18].

Patients with schizophrenia, treated with olanzapine, who were homozygous for the adenine allele of 1438G/A experienced more improvement in their negative symptoms than in patients with other rs6311 genotypes [19]. French patients with schizophrenia, who were treated with olanzapine and other antipsychotic medication with the adenine allele of rs6311, also showed better improvement in their negative symptoms [18].

The cytosine allele of rs6313 and the guanine allele of rs6311 have been associated with higher dyskinesia scores and more disability [20]. The cytosine allele of rs6313 was also associated with a greater likelihood of developing tardive dyskinesia in a Chinese sample [21] and a European sample who were treated with perphenazine [22]. An Italian study also reported an association with tardive dyskinesia and the cytosine allele of 102T/C (i.e., rs6313). In this study, 81% of patients who were homozygous for the cytosine allele of rs6313 were diagnosed with tardive dyskinesia, while 45% of patients with one or more thymine alleles of rs6313 had tardive dyskinesia [23]. While some studies have failed to find this association, a meta-analysis supported the finding that the cytosine allele of rs6313 was associated with tardive dyskinesia [20].

HTR2C

HTR2C is located on the long arm of the X chromosome (e.g., Xq24). Variability in *HTR2C* has been associated with clozapine treatment response. Patients with the cytosine allele of the Cys23Ser SNP (i.e., rs6318) have responded more positively to clozapine. The cytosine allele of the 759C/T SNP (i.e., rs3813929) has also been associated with better response to risperidone in a Chinese sample due to a reduction in negative symptoms [24].

In a small study, an association between the serine allele of rs6318 and tardive dyskinesia has been reported in the female subjects. While there were only two female patients who were homozygous for the serine allele, they both developed tardive dyskinesia [25]. In a different study of men with schizophrenia, the serine allele of rs6318 was also associated with extrapyramidal side effects in patients treated with typical antipsychotic medications for at least 5 years [26].

The cytosine allele of 759C/T (i.e., rs3813929) has been associated with weight gain in patients treated with antipsychotic medications. Patients who were homozygous for the cytosine allele were more likely to gain weight when they were treated with either chlorpromazine or risperidone. None of the patients who had one or more 'protective' copies of the thymine allele of rs3813929 gained more than 7% of their body weight after 6 weeks of treatment [27]. This finding has been replicated in patients treated with olanzapine [28]. Not all studies have reported that the thymine allele of rs3813929 is associated with protection from weight gain, but a meta-analysis of the association between rs3813929 variance and weight gain ultimately concluded that the thymine allele does provide protection from weight gain [29].

DRD2

DRD2 is located on the long arm of chromosome 11 (e.g., 11q23). Clozapine and quetiapine have a relatively low affinity to the *D2* receptor, in contrast to risperidone, aripiprazole, and haloperidol which have a relatively high *D2* receptor affinity [12,30].

DRD2 has been studied for many years and many of the best studied SNPs have been named after the restriction fragment enzyme that was used to initially identify them. Taq1A is now known as rs1800497 and Taq1B is now known as rs1079598. Taq1A has two alleles that are referred to as A1 (i.e., the thymine allele) and A2 (i.e., the cytosine allele). Taq1B has two alleles that are referred to as B1 (i.e., the cytosine allele) and B2 (i.e., the thymine allele). Recently, it has been determined that the Taq1A SNP is actually located in an 'overlapping' gene named *ANKK1*.

The adenine allele of the 241A/G SNP (i.e., rs1799978) has been reported to be associated with more rapid response to risperidone than the guanine allele [31]. Patients with a copy of the guanine allele of the Ser311Cys SNP (i.e., rs1801028) may also respond more rapidly to risperidone than patients who are homozygous for the cytosine allele [32].

An association has been reported between homozygosity of the cytosine allele (i.e., A2) of Taq1A (i.e., rs1800497) and the development of dyskinesia [33]. A combination of homozygosity of the cytosine allele (i.e., A2/A2) of Taq1A and homozygosity of the thymine allele (i.e., B2/B2) of Taq1B (i.e., rs1079598) may be associated with an even greater increased risk of tardive dyskinesia. An independent study of European patients, the cytosine allele (i.e., A2) of Taq1A was again associated with higher risk for the development of tardive dyskinesia [34].

Weight gain has been shown to occur more frequently in patients who are homozygous for the thymine allele (i.e., A1 allele) of Taq1A when compared with individuals who have one or two copies of the cytosine allele (i.e., A2 allele) [35]. It has been proposed that the thymine allele is associated with decreased perception of pleasure or satiety and that this could lead to overeating.

DRD3

DRD3 is located on the long arm of chromosome 3 (e.g., 3q13.3). The serine allele of the Ser9Gly SNP (i.e., rs6280) has been associated with a more positive response to typical antipsychotic medication [36]. In contrast, the thymine allele (i.e., glycine allele) has been associated with a more positive response to atypical antipsychotic medication [37].

Patients with schizophrenia who were treated with olanzapine, who had both the glycine allele of rs6280 and the glycine allele of the 205A/G SNP, have been reported to be more likely to show an improvement in their positive symptoms [38].

Patients with schizophrenia, who were homozygous for the glycine allele of rs6280 and were treated with risperidone, reported better symptom relief than did patients who had one or two copies of the serine allele. In contrast, patients who had both one or more copies of the serine allele of Ser9Gly and who were also homozygous for the cytosine allele of 102T/C of the *HTR2A* gene were quite unlikely to respond to risperidone [39].

Patients who were homozygous for the glycine allele of rs6280 were more likely to develop drug-induced tardive dyskinesia [40] and akathisia [41]. Other studies have supported the association between the glycine allele of rs6280 and tardive dyskinesia [42–45], but

this association has not been universally reported. However, a meta-analysis concluded that the glycine allele of rs6280 was associated with increased risk of tardive dyskinesia [46].

■ *DRD4*

DRD4 is located on the short arm of chromosome 11 (e.g., 11p15.5). Clozapine has been reported to have a low affinity to the *D4* receptor in patients with the glycine allele of the Val194Gly SNP (i.e., rs1800443) [47].

Variations in the 48-bp VNTR in exon 3 have been reported to influence response to antipsychotic medication. Subjects with shorter forms of this VNTR, such as the 4-repeat allele, have been reported to be more likely to respond to typical antipsychotic medication than were subjects with longer forms such as the 7-repeat allele [48]. However, this is not a clinically relevant finding for Chinese patients given that the 7-repeat allele is very rare in the Chinese population [49,50].

Variation in the 48-bp VNTR in the third exon has also been associated with tardive dyskinesia. In an Italian sample, no patients with schizophrenia who were homozygous for the long allele of the 48-bp VNTR polymorphism developed tardive dyskinesia. By contrast, 80% of the subjects who were homozygous for the short allele of the 48-bp VNTR did develop tardive dyskinesia [23].

Clinical implementation

Given that a large number of studies have reported a link between specific gene variants and an increased risk for the side effects of antipsychotic medications, the current challenge is how to integrate these complex findings into a synthetic summation of influences that will provide useful guidance to clinicians. In this review, only those variants that have been reported to be associated with specific outcomes such as weight gain or absence of therapeutic response that result from the use of specific antipsychotic medications are highlighted. For an increasingly large number of these associations, meta-analyses have been conducted in an attempt to resolve conflicting evidence.

The complexity of this literature has led some clinicians to conclude that it is not practical to try to use this knowledge to guide clinical decision making. While it is true that many informative genotypes are only 'actionable' for a relatively small number of specific patients, the cumulative utility of considering many variants simultaneously increases the ability of clinicians to make more rational decisions. To illustrate this integrative process, the following clinical vignette demonstrates how the selection of risperidone, olanzapine and aripiprazole can be facilitated by pharmacogenomic testing. Given that these are three of the most widely used atypical antipsychotic medications, this discussion has practical implications. While this review has considered more than 20 gene-outcome associations, the following illustration will focus on only three associations that have been repeatedly demonstrated.

The first association is that patients with impaired *CYP2D6* metabolic capacity are less likely to tolerate standard doses of *2D6* substrate antipsychotic medications than those patients who have adequate metabolic capacity. The second association is that patients who have an inducible *CYP1A2* genotype will experience substantial shifts in the serum level of *1A2* substrate medications based on their exposure to *CYP1A2* inducers, such as cigarette smoke. The third association is that patients with the homozygous cytosine allele genotype of the 759C/T variant of *HTR2C* will have a higher risk for weight gain when treated with olanzapine and clozapine.

For the purpose of this illustration, all patients are classified as having either a low- or a high-risk genotype for each of these genes. Consequently, a patient might have no high risk genotypes, one high risk genotype, two high risk genotypes, or in the worst case, three high risk genotypes **(Table 3)**.

Using this method, every patient can be classified into one of eight categories. As a consequence of this classification, a psychiatrist can make a more informed decision as to which of these three atypical antipsychotics would provide the greatest likelihood of a good clinical response by considering both the likelihood of side effects and the probability of improvement in target symptoms.

The lowest risk category of the eight possible combinations of these three genotypes would be those patients with adequate *2D6* metabolic capacity, normal *1A2* metabolic capacity that would not be increased by induction and a *HTR2C* genotype associated with a low risk for weight gain. In these patients, all these antipsychotic medications (i.e., risperidone, olanzapine or aripiprazole) would be predicted to be a good choice for treating psychotic symptoms. These patients would be expected to tolerate a standard dose of risperidone. There would be no concern that their olanzapine serum levels would drop if they were exposed to 1A2 enzyme inducers, and they should have an adequate metabolic capacity to metabolize aripiprazole. Finally, they would be able to take olanzapine with a relatively low risk of weight gain.

The highest risk category of the eight possible combinations of these three genotypes would include patients with inadequate *2D6* metabolic capacity,

Table 3. Implications of allelic variability of *CYP2D6*, *CYP1A2* and *HTR2C* for the selection of risperidone, olanzapine or aripiprazole.

Number of risk genotypes	*CYP2D6* metabolic capacity	*CYP1A2* metabolic capacity	*HTR2C*-mediated risk of excessive weight gain	Pharmacogenomically indicated antipsychotic choices: based on the number and implications of three genotypes
0	Normal	Normal	Low	Risperidone, olanzapine, aripiprazole
1	Poor	Normal	Low	Olanzapine, aripiprazole
1	Normal	Inducible	Low	Risperidone, aripiprazole
1	Normal	Normal	High	Risperidone, aripiprazole
2	Poor	Inducible	Low	Aripiprazole
2	Poor	Normal	High	Aripiprazole
2	Normal	Inducible	High	Risperidone, aripiprazole
3	Poor	Inducible	High	Aripiprazole

an inducible *CYP1A2* metabolism, and an increased risk for weight gain based on their *HTR2C* genotype (Table 3). In patients who had all three risk alleles, there would be potential problems with using any of the three atypical antipsychotic medications that we are considering. These patients will have difficulty tolerating standard doses of medications that are *2D6* substrate medications, such as risperidone, and to a lesser degree olanzapine and aripiprazole. These patients would be predicted to experience wide variations in their serum level of olanzapine, as a consequence of exposure to *1A2* inducers. Finally, these patients are very likely to gain weight, which would be particularly problematic if they were treated with olanzapine. A reasonable choice for patients with all of these three problematic genotypes would be aripiprazole as they should be able to tolerate aripiprazole at moderate doses, given that aripiprazole is also metabolized by *3A4*. While these patients will be at some increased risk of weight gain with aripiprazole, this risk is considerably less than their risk of weight gain if they were prescribed olanzapine.

Table 3 provides recommendations for atypical antipsychotic medication selection for all eight clinical risk categories. While a good clinical history can provide some clues as to how these patients should be treated, genotyping provides a rapid, accurate and increasingly cost-effective method to guide the selection and dosing decisions that must be made when treating patients who might benefit from antipsychotic medications.

Currently, panels of many genes are available to clinicians. While having a list of genotypes is better than having no information, it is increasingly clear that laboratory reports will have to provide decision support guidance in order to be able to more effectively implement clinical genotyping. Fortunately, more sophisticated and comprehensible laboratory reports are now available to support clinical decision making [51].

As new research is being reported, it is important to appreciate that our knowledge base regarding how genetic variations affect the response to antipsychotic medications will be evolving. This accumulation of evidence is certain to accelerate with the introduction of more affordable and accurate gene sequencing.

A decade ago, there was no pharmacogenomic guidance available to psychiatrists. The introduction of testing to identify variants in a single gene provided clinicians an initial opportunity to be better able to select an antipsychotic medication that their patients could adequately metabolize. Gradually, more and more gene variants that predict the risk for side effects have been added to panels to further improve tolerability and safety of treatment with antipsychotic medications. Of course, clinicians still do not know with certainty how their patients will respond to a given medication, but they can provide more rational treatment. Given current available genotyping capacity, pharmacogenomic testing can be used to minimize the occurrence of serious side effects in patients who are treated with antipsychotic medications. Within the next 5 years, pharmacogenomic testing prior to the prescription of an antipsychotic will become the standard of care.

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Executive summary

CYP2D6
- Risperidone and iloperidone are atypical antipsychotics and chlorpromazine, thioridazine, perphenazine and haloperidol are typical antipsychotics that are primarily metabolized by the 2D6 enzyme.

CYP1A2
- Clozapine and olanzapine are predominantly metabolized by the CYP1A2 enzyme.

SLC6A2
- In patients with schizophrenia, patients with one or two copies of the thymine allele of rs2242446 were more likely to respond positively to risperidone and olanzapine.

HTR1A
- Patients with the cytosine allele of 1019C/G have been reported to have greater improvement in negative symptoms when treated with risperidone and olanzapine than patients with the guanine allele.

HTR2A
- Patients who are homozygous for the adenine allele of rs6311 are more likely to respond to clozapine and risperidone.
- The cytosine allele of rs6313 has been associated with tardive dyskinesia.

HTR2C
- The cytosine allele of the *HTR2C* Cys23Ser single nucleotide polymorphism (SNP) has been associated with better response to clozapine.
- The serine allele of the *HTR2C* Cys23Ser SNP has been associated with tardive dyskinesia.
- The cytosine allele of the -759C/T SNP of *HTR2C* has been associated with weight gain in patients treated with many antipsychotic medications.

DRD2
- The *DRD2* Taq1A A2 allele and the *Taq1B* B2 allele have been associated with the development of tardive dyskinesia.
- The *DRD2* Taq1A A2 allele has also been associated with weight gain.

DRD3
- The *DRD3* glycine allele of the Ser9Gly SNP was associated with better response to both olanzapine and risperidone.
- The *DRD3* glycine allele of the Ser9Gly SNP was associated with a greater risk of developing drug-induced tardive dyskinesia and akathisia.

DRD4
- The *DRD4* 4-repeat allele of the 48 bp variable number tandem repeat has been reported to be more likely to respond to typical antipsychotic medication in some patients.
- The *DRD4* shorter repeat alleles of the 48 bp variable number tandem repeat has been associated with a greater risk of tardive dyskinesia.

Clinical implementation
- Identifying only three pharmacogenomically relevant genotypes that predict pharmacogenomic risk phenotypes can increase the probability of selecting an antipsychotic with a greater likelihood of response when considering the choice of risperidone, olanzapine or aripiprazole.

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