Published in final edited form as:
Pharmacotherapy. 2014 February ; 34(2): 166–184. doi:10.1002/phar.1398.

Pharmacogenomic Testing for Neuropsychiatric Drugs: Current Status of Drug Labeling, Guidelines for Using Genetic Information, and Test Options

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Abstract

Advancements in pharmacogenomics have introduced an increasing number of opportunities to bring personalized medicine into clinical practice. Understanding how and when to use this technology to help guide pharmacotherapy used to treat neuropsychiatric conditions remains a challenge for many clinicians. Currently, guidelines exist to assist clinicians in the use of genetic information for drug selection and/or dosing for the tricyclic antidepressants, carbamazepine, and phenytoin. Additional language in the product labeling suggests that genetic information may also be useful for assessing the starting and target doses, as well as drug interaction potential, for a number of other medications used to treat psychiatric and neurological conditions. In this review, we outline the current status of pharmacogenomic testing for neuropsychiatric drugs as it pertains to information contained in drug labeling, consensus guidelines, and test panels, as well as considerations related to obtaining tests for patients.

Keywords

Pharmacogenetics; pharmacogenomics; CYP2D6; CYP2C19; antidepressants; antipsychotics; Stevens-Johnson syndrome; pharmacogenetic testing

Advances in pharmacogenomics have introduced an increasing number of opportunities to bring personalized medicine into clinical practice. Personalized medicine may be defined as "a comprehensive, prospective approach to preventing, diagnosing, treating and monitoring disease in ways that achieve optimal individual health care decisions."[1] One way that providers may personalize certain treatments is through pharmacogenomic testing for individual genetic variants that may influence response, tolerability, or safety of medications. Over 100 medications now contain United States Food and Drug Administration (FDA) labeling related to potentially applicable pharmacogenomic biomarkers.[2] Consortia are now in place to systematically evaluate the literature and data for specific drugs or groups of drugs with the overarching goal of creating guidelines for testing and how to clinically implement genetic tests. At the time of this publication, the top three therapeutic areas represented by drugs with the FDA labeling are oncology (32 drugs), psychiatry/neurology (32 drugs; Table 1) and cardiovascular medicine (10 drugs).[2]

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Disclosures:
The opinions expressed in this article are solely those of the authors. Dr. Bishop serves as an advisory board member for Physician's Choice Laboratory Services.

Understanding and applying pharmacogenomic testing in psychiatry and neurology has been complex. Genetic variables influencing the pharmacokinetics and pharmacodynamics of some of these medications have been described; however, currently lacking are large and controlled studies specifically designed to assess whether using this information to inform drug selection and/or dosing is better than clinical care.[3] These types of studies are difficult to design and execute because of multidimensional biological causes of psychiatric diseases and limited knowledge of the mechanisms of action of neuropsychiatric medications.[4] However, inadequately choosing and dosing neuropsychiatric medications can have serious consequences. Thus, any added knowledge that can help clinicians optimize the risk:benefit ratios of our available treatments has tremendous potential for improving the lives of patients. Despite these barriers, drug labeling and consensus guidelines now provide language regarding the potential clinical utility of pharmacogenomic testing. Additionally, available test panels and laboratory services now include assays to assess gene variants mentioned in product labeling as well as other markers. How clinicians may decide to recommend, order, and use this information has not been well studied, and not all clinicians are familiar with the interpretation of genetic tests or how to explain results to their patients. Thus, the purpose of this review is to outline the current status of pharmacogenomic testing for neuropsychiatric medications as it pertains to drug labeling, guidelines, and testing panels, as well as considerations related to actually obtaining tests for patients. It is our expectation that shedding some light on the consensus and controversies surrounding the application of pharmacogenomic testing for neuropsychiatric medications will help clinicians understand and apply current knowledge as well as provide a foundation on which new information can be built to evolve testing guidelines and recommendations.

Historical Perspectives

The 1950s marked the beginning of our modern conceptualization of pharmacogenetics as a distinct discipline. In 1959, the German human geneticist Friedrich Vogel first introduced the term “pharmacogenetics.”[5] Since then, many researchers have used genetic techniques to examine variability in drug response across patients and populations. One of the first known studies in psychiatry identifying a potential inherited basis of drug response summarized an investigation of 41 first-degree relative pairs treated with tricyclic antidepressants (TCAs).[6] Thirty-eight of the 41 relative pairs were concordant for response. In the 1960s and early 1970s, Pare et al. demonstrated that subgroups of relatives followed in assessments of antidepressant treatment response exhibited striking similarities in their outcomes to treatment.[7, 8] In these rare instances where family members were assessed, all 12 first-degree relative pairs receiving monoamine oxidase inhibitors (MAOIs) and 10 of 12 first-degree relatives receiving TCAs were concordant for response. Around the same period, Alexanderson et al. investigated steady-state plasma concentrations of nortriptyline in twins and postulated that the variability observed in the data could be due to genetic differences in ability to metabolize the drug.[9] In 1994, O’Reilly et al. described eight family members diagnosed with depression who showed a similar pattern of response to tranylcypromine and lack of response to TCAs or various new-generation agents.[10] Even though at that time the biochemical mechanisms of familial response were unknown, genetic variations in the metabolism of antidepressants were suspected. These hereditary studies provided the first evidence that genetic factors may account for some of the variability seen in drug response among patients with psychiatric conditions.

Early observations from pharmacokinetic studies in psychiatry paved the way for drug metabolism and molecular genetic studies that began to more clearly identify and characterize genetic mechanisms that may influence drug outcomes. As was the case with many other therapeutic areas, differences in drug metabolism were initially identified. In the mid-1970s, Smith et al. studied response to the antihypertensive drug debrisoquine[11] and

observed that subjects' drug responses could be separated into two distinct populations, extensive metabolizers and nonmetabolizers. The drug concentrations exhibited a binomial distribution, and since this discovery, debrisoquine has commonly been used as a probe drug for predicting cytochrome P450 (CYP) 2D6 enzyme activity. Subsequently, a number of research groups have investigated gene variants related to the pharmacodynamics of neuropsychiatric medications. Examples include serotonin$_{2A}$ receptor (*HTR2A*) and dopamine^{2} receptor (*DRD2*) variants related to antipsychotic response[12] and serotonin transporter and antidepressant response,[13] as well as others outlined in a recently published review by the European Group for the Study of Resistant Depression (GSRD).[14] Similar studies were conducted to investigate adverse effects, where an association between a common serotonin transporter polymorphism and antidepressant-induced mania was described.[15] Additionally, a significant concordance among first-degree relatives for antipsychotic-induced tardive dyskinesia was described by Müller et al.[16] and antipsychotic-induced weight gain by Gebhardt et al.[17]

Translation of science to clinical practice in psychiatry has begun only recently. Limitations have included lack of clear relationship between the serum concentrations of many neuropsychiatric drugs and efficacy, a relatively wide therapeutic window for many of these medications, lack of pharmacogenomic guidelines, and a limited number of trials investigating pharmacogenomic testing in ways that can be translated to the clinical practice. In addition, many psychiatric and neurological diseases are thought to be polygenetic and multifactorial in etiology, with multiple medication classes commonly used to manage symptoms. This further complicates our understanding of how and when to use testing in clinical environments.

Current Status of Drug Labeling and Pharmacogenomic Testing Guidelines

Currently, there are 110 medications with pharmacogenomic biomarker information listed in the product labeling.[2] Examples of neuropsychiatric medications with this information are listed in Table 1. Of the 32 neuropsychiatric medications listed, 27 (84%) have CYP2D6 metabolizer status listed as an important biomarker, 3 (9%) identify CYP2C19 metabolizer status as an important biomarker, and 3 (9%) pertain to other genetic markers (e.g., major histocompatibility complex human leukocyte antigen (HLA) allele *HLA-B*1502* for carbamazepine and phenytoin, carbamoyl phosphate synthetase 1 [*CPS1*] and ornithine carbamoyltransferase [*OTC*] for valproic acid). Of the 32 neuropsychiatric medications listed, 10 have information related to dosing, precautions, or warnings (Table 1). Dosage changes for known poor metabolizers (PMs) for CYP2D6 or CYP2C19 are outlined for aripiprazole, atomoxetine, citalopram, clobazam, iloperidone, pimozide, and tetrabenazine. At the time of this review, carbamazepine had genetic information listed in the black-box warning section of the label, which was limited to the patients of Asian ancestry.

One challenge with clinically applying pharmacogenomic information relates to a lack of guidance of how one should use this information, even though multiple approaches have been taken to establish guidelines. In 2001, Kirchheiner et al. published a comprehensive review of available pharmacogenomic studies of antidepressant drugs metabolized by CYP2D6 and CYP2C19 enzymes.[18] Based on these data (representing data published between 1997 and 2003), the authors calculated a percentage dose adjustment recommended for each metabolizer category. This publication was one of the first that aggregated information to highlight and provide pharmacokinetic justification for dosage adjustments. This information was provided in a way that suggested drug-specific dosage adjustments based on changes in pharmacokinetic parameters known to result from differences in metabolizer status (e.g., PMs of CYP2C19 should receive 60% of the average dose of citalopram). In 2006, de Leon et al. published clinical guidelines for psychiatrists regarding

pharmacogenomic testing for *CYP2D6* and *CYP2C19.*[19] The authors provided general information about the availability of genetic testing, information about choice of appropriate test, and dose recommendation for antidepressants and antipsychotic drugs metabolized by CYP2D6 and CYP2C19. Their recommendations were designed as dosing or drug selections suggestions based on the results of testing as well as other clinical factors.

Efforts to more formally develop testing guidelines were extended by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group in 2007.[20] This initiative was established by the Centers for Disease Control (CDC) Office of Public Health Genomics in 2004, with the goal of establishing and evaluating evidence for pharmacogenomic testing in a systematic manner. To date, the only assessment of neuropsychiatric medications conducted by this group was an examination in 2007 of evidence for *CYP2D6* testing in adults with nonpsychotic depression who were being considered for treatment with a selective serotonin reuptake inhibitor (SSRI). [20] After reviewing the available evidence, the panel concluded that pharmacogenomic testing in adults initiating SSRI treatment for depression was not recommended at that time (2007). Furthermore, the EGAPP initiative could not endorse the clinical utility of pharmacogenomic testing for SSRIs and identified the need for additional prospective, double-blind clinical trials to expand the evidence in support of pharmacogenomic testing.

The above recommendations were followed by a publication from the Royal Dutch Association for the Advancement of Pharmacy. The Pharmacogenetic Working Group (PWG), established by this association, developed guidelines that are available on the Pharmacogenomics Knowledgebase (PharmGKB) Web site (www.pharmgkb.org).[21] The PWG publication includes 85 genotype and phenotype drug combinations for 25 medications. At this time, the drug-gene recommendations included on the PharmGKB site provide information for 17 psychiatric drugs as they relate to variants in the *CYP2D6* gene. The number of guidelines for the *CYP2C19* gene and neuropsychiatric medications is significantly lower (only one guideline). The PWG guidelines translate the phenotype and genotype information into therapeutic dose recommendations. In addition, information about clinical relevance is provided with the clearly stated level of the evidence (e.g., strong, moderate, and optional). PWG recommendations are designed to inform clinicians about dosage adjustments or drug choices in situations when genetic results are available.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was established in 2009 and consists of members from the Pharmacogenomics Research Network (PGRN), Pharmacogenomics Knowledge Base (PharmGKB) affiliates, and experts in the area of pharmacogenomics.[22] The consortium was formed in order to establish evidence-based guidelines and to disseminate them to clinicians. These peer-reviewed guidelines are published and are readily available on the PharmGKB Web site and represent comprehensive and up-to-date assessments of this topic at this time. They are designed to assist and guide drug therapy in situations when genetic information is available, but they do not specifically advocate for if and for whom tests should be obtained. Currently, there are 10 published guidelines. With respect to neuropsychiatric medications, guidelines for TCAs, SSRIs, carbamazepine, phenytoin, and valproic acid are either published or are in progress (www.pharmgkb.org). The following sections in this review summarize initial guidelines for neuropsychiatric medications as well as other selected agents with product labeling that has incorporated actionable pharmacogenomic information (e.g., dosing recommendations) into the warning or dosing sections with relevance to patient safety. For other drugs, a summary of the labeling information is included in Table 1.

Guidelines and Labeling for Tricyclic Antidepressants

Tricyclic antidepressants are used for a variety of conditions including depression and neuropathic pain. Language regarding the pharmacokinetic effects of PM status for CYP2D6 and/or CYP2C19 is included in the product labeling for clomipramine, desipramine, doxepin, imipramine, nortriptyline, protryptyline, and trimipramine.[23] Although the details of the labeling may differ slightly across medications, the wealth of evidence linking metabolizer status to serum concentrations and drug outcomes provided the basis for guidelines that now outline how to use available pharmacogenomic test information in clinical scenarios.[24] The recommendations are based on a comprehensive literature review with a focus on the pertinent genotypes and available pharmacokinetic data based on the genotype and phenotype characteristics.

TCAs (e.g., amitriptyline, clomipramine, doxepin, imipramine, and trimipramine) undergo demethylation by CYP2C19 followed by hydroxylation by CYP2D6 (metabolites of the above medications with the addition of desipramine and nortriptyline).[25] Polymorphisms in one or both genes may alter drug metabolism and therefore symptom response as well as dose-related adverse effects. Based on available data, the guidelines recommend a 50% dose reduction of amitriptyline and nortriptyline in persons who are CYP2D6 or CYP2C19 PMs.[24] For CYP2D6 ultrarapid metabolizers (UMs), therapy with amitriptyline or nortriptyline should be avoided, or the initial target dose should be increased. For CYP2C19 UMs, alternative therapy should be considered, but the evidence supporting this recommendation was recognized as being not strong at this time. In situations when a patient is a CYP2D6 intermediate metabolizer (IM), the guidelines note that clinicians could reduce the initial dose by 25%, but the level of evidence supporting this recommendation is not as strong as that for PM status. It should be recognized that TCAs are categorized based on their chemical structure into two categories: secondary and tertiary amines. Differences in their chemical structure dictate affinity to neurotransmitters. Tertiary amines (e.g., amitriptyline) have more pronounced serotonergic activity whereas secondary amines (e.g., nortriptyline) have more pronounced noradrenergic activity.[26] Chemical structure also influences which enzymes are preferentially involved in metabolism and influences the overall ratio of tertiary to secondary amine plasma concentration ratio, clearance, and adverse-effect profile. The guidelines note that recommendations available for amitriptyline and nortriptyline may be applied to other tricyclic antidepressants, using the rationale that TCAs as a class have very similar pharmacokinetic profiles, and amitriptyline and nortriptyline are model drugs for each of their respective amine categories.[24] However, the relationships between pharmacogenomic markers and serum concentrations or treatment outcomes have not been extensively studied with the other tricylic agents.

Guidelines and Labeling for Carbamazepine

Carbamazepine is used for the treatment of epilepsy and is commonly used as a mood stabilizer for bipolar spectrum disorders.[23] Recently published CPIC guidelines strongly support *HLA-B*1502* genotyping for patients of Asian ancestry who are being considered for the treatment with carbamazepine.[27] CPIC guidelines followed changes to the product labeling in 2007, which incorporated the use of pharmacogenomic testing into the black-box warning section.[23] This warning highlights the risk of severe and potentially fatal dermatologic reactions, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Both the FDA labeling and CPIC guidelines recommend genetic testing for presence of the *HLA-B*1502* allele in patients of Asian ancestry.[23, 27] The guidelines for testing highlight distinct ethnic and regional differences in the distribution of the risk allele that should be considered when evaluating who should be tested. The *HLA-B*1502* polymorphisms are found in the highest frequencies in Asian populations (10–15% in patients from China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan; 2–4% in

patients from south Asia and India), with extremely low or nonexistent(<0.01%) in patients of European, Hispanic, Native American, and African descent.[28] The *HLA-B*1502* allele appears to cosegregate with two polymorphisms (rs2844682 and rs3909184) that are thought to result in altered immune system recognition to carbamazepine that bypasses antigen processing involved in direct presentation to cytotoxic T cells and subsequent cytotoxicity.[29]

There are other HLA alleles that also demonstrate evidence for the association with carbamazepine-induced hypersensitivity reactions, including mild maculopapular eruptions, drug hypersensitivity syndrome, SJS, and TEN. One additional variant allele, *HLA-A*3101*, was first identified in Han Chinese, followed by identification among Japanese, European, and Korean populations.[30] Currently, recommendations provided by the CPIC and in the FDA labeling do not include these additional HLA variants.

In line with the available evidence, guidelines, and labeling, carbamazepine may be used in non-*HLA-B*1502* carriers. In the case of those who carry one or two copies of *HLA-B*1502* alleles (*HLA-B*1502* positive), alternative agents should be considered. Clinicians should bear in mind that alternative agents (phenytoin, fosphenytoin, oxcarbazepine, eslicarbazepine acetate, and lamotrigine) also show evidence of hypersensitivity reactions in carriers of the *HLA-B*1502* allele.[27] For *HLA-B*1502*-positive patients who previously received carbamazepine for period of more than 3 months, a therapeutic switch is optional since the highest risk of the development of dermatologic complications occur in the first months of the therapy.[31,32] A meta-analysis of studies published as of 2011 identified that the specificity and sensitivity of *HLA-B*1502* testing were 0.88 and 0.96, respectively. Across studies, the odds of SJS or TEN were 113.4 times greater in *HLA-B*1502* carriers compared with noncarriers.[30]

Labeling for Phenytoin

The FDA labeling recommendations for carbamazepine were followed by the inclusion of similar information in the warning section of the product labeling for phenytoin highlighting the risk of severe and potentially fatal SJS or TEN.[23] The FDA recommends genetic testing for the presence of the *HLA-B*1502* allele in patients of Asian ancestry who are being considered for therapy with phenytoin. Testing recommendations for phenytoin are based on literature describing SJS and TEN, as well as the presence of an aromatic ring which has a similar structure to carbamazepine.[33] However, the genetic association of *HLA-B*1502* and SJS or TEN development may be more complex in the case of phenytoin. A case-control association study identified that additional variants (*HLA-B*1301*, *Cw*0801*, and *DRB1*1602*) may also be associated with development of phenytoin induced SJS and TEN.[33] Sensitivity and specificity values for *HLA-B*1502* testing from a meta-analysis of studies published as of 2012 were 36.6% and 87.2%, respectively, perhaps indicative of additional factors influencing phenytoin-associated risk for SJS and TEN.[34]

In addition to the recommendation for *HLA-B*1502*-positive subjects, the Dutch Pharmacogenetics Working Group provides dose recommendations for carriers of *CYP2C9* variants in patients treated with phenytoin, which is a major substrate for this metabolic pathway.[35] This recommendation outlines a 25% dose reduction for *CYP2C9*1/*2* or *1/*3* and a 50% dose reduction for *2/*2*, *2/*3*, or*3/*3* carriers. However, this recommendation is not reflected in the latest phenytoin drug label.

Labeling for Selective Serotonin Reuptake Inhibitors

SSRIs are first-line therapies for the treatment of depression, some anxiety disorders, forms of posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). The therapeutic window is thought to be wide for SSRIs with respect to treating depression and

anxiety.[36] However, for other disease states, such as OCD, there is often a need for higher doses, which can pose a challenge for identifying target doses and titration strategies that must balance the risks of dose-dependent adverse effects with the benefits of dose-dependent response.[37] As SSRIs have broad therapeutic windows, use of genetic testing that has implications for dose-related outcomes is controversial. The CYP enzymes, primarily CYP2D6 and CYP2C19, are involved in the metabolism of SSRIs. Moreover, citalopram, fluoxetine, fluvoxamine, and paroxetine are strong inhibitors of CYP2D6 and/or CYP2C19 (citalopram).[38]

The differences in pharmacokinetic parameters between metabolizer groups have been recognized for citalopram and fluvoxamine. The FDA label for citalopram recommends a maximum dose of 20 mg/day in known PMs.[23] Regarding fluvoxamine, the FDA labeling recommends caution when the drug is administered to PMs or when it is coadministered with CYP2D6 inhibitors.[23] Labeling for fluoxetine and paroxetine include only general information in the drug-drug interaction section, in view of the fact that both agents have the ability to inhibit CYP2D6.[23]

As previously mentioned, an initial evaluation of literature by the EGAPP in 2007 came to the conclusion that there was insufficient evidence to support CYP pharmacogenomic testing for SSRIs.[20] Since that time, research in this area has continued with some studies suggesting beneficial effects of certain pieces of pharmacokinetic and pharmacodynamic test information when applied in clinical practice scenarios.[39] Despite this optimism, uncertainty and challenges still exist in identifying the genetic components of SSRI response.[40] At the time of this review, a reevaluation of SSRI evidence is currently underway that will hopefully provide more up-to-date guidance for these medications.

Labeling for Valproic Acid

Recently, it has been recognized that rare mutations in the urea cycle genes encoding *CPS1* and *OTC* might have detrimental consequences in patients being treated with valproic acid. Severe cases of urea cycle disorders (UCDs) are primarily recognized in newborn infants. These infants may develop lethargy, poor feeding, and emesis on initiation of protein in their diet.[41] If unrecognized or untreated, accumulation of ammonia may cause cerebral edema, followed by coma and possibly death. Additionally, cases of severe hyperammonemia have been reported after the administration of valproic acid in pediatric populations.[42] In cases of partial UCD deficiencies, increased levels of accumulating ammonia might be triggered by dehydration, stress, or administration of valproic acid.[43] The FDA-approved drug label includes a contraindication of valproic acid in patients with known UCDs as well as provides information regarding those who should be considered for additional evaluation.[23] Although there are genetic variants in the *CPS1* and *OTC* genes that are associated with UCDs, genotyping for these variants before the initiation of valproic acid therapy is not recommended at this time. This is perhaps due to the general early recognition of these disorders, which would theoretically result in a relatively low number of previously unidentified patients discovered as part of clinical genetic testing.

Labeling for Tetrabenazine

In August 2008, tetrabenazine was approved by the FDA for the treatment of movement disorders associated with Huntington's disease.[23] It has also been investigated as a possible treatment for antipsychotic-associated tardive dyskinesia and other hyperkinetic movement disorders.[44] In the case of tetrabenazine, pharmacogenomic testing could be highly relevant since the parent drug and its equivalently active metabolites are primarily metabolized by CYP2D6.[45] In the initially approved labeling, genetic testing information was included with the recommendation that genetic testing for *CYP2D6* be completed prior to the initiation of

the tetrabenazine treatment with daily doses exceeding 50 mg.[23] This information appears to be based on a small number (n=2) of PMs profiled in pharmacokinetic studies during drug development, with further justification from pharmacologic CYP2D6 drug inhibition studies. These studies suggest robust differences in the pharmacokinetics of the drug in PMs. A subsequent investigation that included adverse-effect assessments identified trends suggesting more adverse events (i.e., sedation, akathisia, insomnia, and suicidality) in PMs.[45] Although not statistically significant, they may still be clinically meaningful. The adverse events experienced included drowsiness, akathisia, parkinsonism, confusion, and depression.

Labeling for Other Neuropsychiatric Drugs

Several other neuropsychiatric drugs also include pharmacogenomic biomarker information in the FDA product labeling. This information is relevant to the warning, clinical pharmacology, drug interactions, and dosage and administration sections of the label. As highlighted in Table 1, the specificity and usefulness of pharmacogenomic language found in the product labeling is highly variable. The most refined examples include recommendations about dosing in patients of a specific metabolizer category if genetic information is known. Examples include atomoxetine, aripiprazole long-acting injection, clobazam, and iloperidone. The product labeling for many other medications may include information about the impact of CYP2C19 or CYP2D6 metabolizer status on the pharmacokinetic parameters of a drug or potential importance for drug interactions. No labeling or guidelines currently mandate that pharmacogenomic testing be performed; rather, they provide varying levels of recommendations for what implications that information may have if it is available.

How and Where Pharmacogenomic Testing Should Be Performed

Despite the challenges of understanding how and when to perform pharmacogenomics tests when prescribing neuropsychiatric drugs, its clinical use is increasing. Similarly, so are the options for obtaining pharmacogenomic tests. In 2004, the FDA approved the first pharmacogenomic testing platform—the Roche AmpliChip CYP450 Genotyping Test (Roche Molecular Systems Inc. and Affymetrix Inc., Pleasanton, CA), for *CYP2D6* and *CYP2C19*—which facilitated the availability of genetic testing at multiple clinical centers.[46] Since then, several companies have introduced testing panels to the market and have offered them to physicians or directly to potential customers. These innovations changed the arena of genetic testing and revealed the need for development and implementation of support systems such as pharmacogenomic education to clinicians, guideline development, and performance of large, randomized clinical trials.

Pharmacogenomic testing platforms and laboratory services include those approved by the FDA as well as those developed and/or provided in Clinical Laboratory Improvement Amendments–certified laboratories. Although there will be an increasing number of resources available to prescribers and patients to obtain this information, it is important to understand some of the variables that may differ across available options—that not all testing platforms or services examine the same variants in a given gene and that these differences may be more or less important depending on the ancestry of a particular patient. As they relate to the neuropsychiatric medications reviewed in this article, a number of testing platforms and testing facilities currently exist that may be helpful in examining the variants that are relevant to these medications. As an example, a selection of the pharmacogenomic testing platforms or laboratories relevant to the biomarkers listed in guidelines or product labeling in the United States is listed in Table 2. Some testing options are directly available to customers and do not require physician involvement (e.g., 23 and Me, Matrix Genomics) and others, which call for a physician order (e.g., Genelex,

AssureRx). Whereas this list and perhaps details of the individual platforms will certainly change, highlighting some similarities and differences may be helpful in identifying sources of variability in available resources and how they may relate to specific clinical scenarios.

The information included in Table 2 illustrates that currently available platforms relevant to pharmacogenomic testing for neuropsychiatric medications encompass a range of gene variants or alleles that are genotyped. This introduces some limitations when assigning genotype-inferred phenotypes. Since the list of genotyped alleles and possible copy number variation is not comprehensive for all platforms, the assigned phenotype is predicted to the best of available knowledge and may be a source of discrepancies between platforms. For example, if a given platform is unable to assess *CYP2D6* gene duplication, important information predicting UMs can be easily missed. Additionally, the star (*) nomenclature commonly used for assigning allele status for drug-metabolizing enzyme genes defaults to the wild-type or **1* allele in the absence of a variant. Thus when a specific variant is not tested, there is the risk of misclassification of the **1* allele.

Race-ethnicity is an important factor that may influence drug response through gene variants and may be observed at different frequencies depending on one's ancestry.[47] Racial-ethnic variation needs to be recognized and taken into the consideration during the selection process of an appropriate genetic test panel. Different racial or ethnic groups may not only vary in the frequency of a given variant identified as important for pharmacogenomic testing but may also carry other, different variants not identified or included in current tests. Generally speaking, CYP2D6 PM status is most commonly observed in Caucasians (~10%), is relatively infrequent in Asians (0–1.2%), and differs widely in African-Americans (ranging from 1.9–7.3%).[48, 49] Among American populations, UMs have been observed at similar frequencies in Caucasians and African-Americans (4.3% and 4.9%, respectively).[48, 49] UMs are rarely seen in persons of Asian descent. The highest frequency of UMs has been described in persons from Saudi Arabia (20%)[50] and Ethiopia (16%).[51] Pronounced racial-ethnic differences are also observed in the frequencies of CYP2C19 genotypes and phenotypes. PMs are most commonly observed in those of Asian ancestry (~20%), whereas PMs are less frequent in African-Americans (4.5%) and Caucasians (2.3%).[48, 49] The significant influence of race-ethnicity was described previously in the context of carbamazepine use and development of severe dermatologic adverse events in *HLA-B*1502* carriers in subjects of Asian descent.[28] Thus, the magnitude of variability across populations is highly gene and/or polymorphism specific. These examples clearly illustrate the necessity of appropriate test selection in the perspective of the ancestry of the patient.

In examining available platforms, many of the differences that exist represent the inclusion or exclusion of rare alleles that may influence metabolizer status (e.g., *CYP2D6*69*, *CYP2D6*36+*10*) or more common alleles that may result in reduced or partial gene expression that contribute to IM status for which the clinical implications are not as easily defined. Additionally, testing services and platforms may provide results differently to patients and providers, and thus the "usability" of the results is an important consideration in how of if they may be used and interpreted correctly in the context of a specific patient's disease states and medication regimen.

Moreover, multiple platforms offer testing of several polymorphic variants for which guidelines and labeling do not exist. Examples include variants in the serotonin transporter (*SLC6A4*), *HTR2A*, serotonin$_2$ receptor (*HTR2C*), catechol-*O*-methyltransferase (*COMT*), and *DRD2*, as well as others. Variants in these genes have been extensively studied as candidates that may influence drug response, psychiatric disease risk, or disease-related phenotypes. Evidence exists to support hypotheses that these variants may influence

response or adverse effects to psychiatric medications. However, the effect sizes for these outcomes seem to be small to moderate at best, with heterogeneity across studies and patient populations that needs to be resolved before clinical application becomes widespread. These statements of effect size and heterogeneous results may arguably be applicable to studies of drug metabolism markers. However, variation at these loci, which are more related to drug pharmacodynamics, have also been associated with disease risk, personality traits, or other psychiatric phenotypes that require important consideration as they relate to what the results may mean to the patient and their relatives.

Implications for Clinical Practice

Pharmacogenomics is now beginning to reach clinical practice in neuropsychiatric settings. Currently, guidelines exist to help clinicians in the use of existing genetic information to direct drug selection and/or dosing in the TCA class of antidepressants, carbamazepine, and phenytoin. Additional language in the product labeling suggests that genetic information may also be useful for assessing the starting and target doses and drug interaction potential for a number of other medications such as antidepressants and antipsychotics. Most of the information that has been formally assessed relates to variability in drug-metabolizing enzymes. Variants influencing immune response are notable for influencing the risk for severe dermatological reactions from carbamazepine and phenytoin.

Published guidelines and updates to the U.S. product labeling represent significant advances to our ability to implement pharmacogenomic testing into clinical practice and how to use some this information when it is available. However, information to support whether testing should be completed for gene variants that influence drug metabolism is still lacking. The lack of data examining whether patient care that integrates pharmacogenomic test information for many of these drugs results in better or safer treatment outcomes remain a significant barrier to widespread use and coverage by insurance providers. As of 2012, 8 of 27 reviewed pharmacogenomic tests, including carbamazepine and tetrabenazine, were covered by leading U.S. insurance companies.[52] The covered tests included *CYP2D6* for tetrabenezine and *HLA-B*1502* for carbamazepine. The coverage policies were mostly based on the evidence included in pharmacogenomics guidelines and FDA-approved product labeling. This indicates that as guidelines and labeling increase, so will the likelihood of reimbursement. Certainly, there are many clinical examples that highlight individual instances where using such information has provided knowledge that improved care; however, how testing performs on a larger scale is still uncertain, despite the biological plausibility of the data supporting the labeling and guidelines discussed in this review. Until this knowledge gap is addressed, extensive use will continue to be controversial.

Conclusion

Despite the controversies regarding when and whether to obtain pharmacogenomic testing, the improvements in technology supporting these tests, improved accessibility of testing options, and the growing number of resources that help clinicians understand how to use this information when it is available are making this aspect of personalized or precision medicine a reality. Thus, it is important for providers to become more aware of the science and clinical relevance of pharmacogenomic tests. Additionally, multiple options exist that may be used for testing, not all tests interrogate the same genetic variants, and some of these differences may have important clinical consequences. Continuing the education of established providers as well as clinical trainees is an important step in this process, which will continuously evolve as technology and clinical evidence informing testing and application are advanced.

Acknowledgments

Acknowledgments/Support:

Dr. Bishop is supported by a grant (K08MH083888) from the National Institute of Mental Health. Dr. Müller is supported by a Brain & Behavior Research Foundation Award, a Canadian Institutes of Health Research Michael Smith New Investigator Salary Prize for Research in Schizophrenia, an Ontario Mental Health New Investigator Fellowship, and an Early Researcher Award by the Ministry of Research and Innovation of Ontario, Canada.

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Table 1

Language Included in the U.S. Food and Drug Administration Product Labeling for Neuropsychiatric Drugs

Drug or Drug Combination	Pharmacogenomic Biomarker	Label Section	Label Information[23]
Citalopram	CYP2C19, CYP2D6	Drug Interactions, Warnings	The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 PMs due to the risk of QT prolongation. Citalopram steady state levels were not significantly different in PMs and EMs of CYP2D6. (Revised 12/03/2012)
Clobazam	CYP2C19	Clinical Pharmacology, Dosage and Administration, Use in Specific Populations	In CYP2C19 PMs, levels of *N*-desmethylclobazam, clobazam's active metabolite, will be increased. Therefore, in patients known to be CYP2C19 PMs, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight…If necessary…an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21. Concentrations of clobazam's active metabolite, *N*-desmethylclobazam, are higher in CYP2C19 PMs than in EMs. The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active *N*-desmethylclobazam. Compared to CYP2C19 EMs, *N*-desmethylclobazam AUC and C_{max} are approximately 3–5 times higher in PMs (e.g., subjects with $^{*}2/^{*}2$ genotype) and 2 times higher in IMs (e.g., subjects with $^{*}1/^{*}2$ genotype). The prevalence of CYP2C19 PM differs depending on racial/ethnic background. Dosage in patients who are known CYP2C19 PMs may need to be adjusted. The systemic exposure of clobazam is similar for both CYP2C19 PMs and EMs. (Revised 12/2012)
Diazepam*	CYP2C19	Drug Interactions Clinical Pharmacology	The marked interindividual variability in the clearance of diazepam reported…is probably attributable to variability of CYP2C19. (Revised 09/2010)
Aripiprazole	CYP2D6	Clinical Pharmacology, Dosage and Administration	The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose and then adjusted to achieve a favorable clinical response. …PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure…compared to EMs. …The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs, respectively. (Revised 02/2012)
Aripiprazole, extended-release injectable suspension	CYP2D6	Clinical Pharmacology, Dosage and Administration	Dosage adjustments are recommended in patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days…PM-adjusted dose 300 mg; PM and taking concomitant CYP3A4 inhibitors-adjusted dose 200 mg. (Revised 02/2013)
Atomoxetine	CYP2D6	Dosage and Administration, Warnings, Precautions, Drug Interactions, Clinical Pharmacology	PMs of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA [atomoxetine] compared with EMs…The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA. In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, or in patients

Pharmacotherapy. Author manuscript; available in PMC 2015 February 01.

Drug or Drug Combination	Pharmacogenomic Biomarker	Label Section	Label Information[23]
			who are known to be CYP2D6 PMs, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. (Revised 08/16/2012)
Carbamazepine	*HLA-B*1502*	Boxed Warning, Warnings, Precautions	Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of *HLA-B*1502*, an inherited allelic variant of the *HLA-B* gene. *HLA-B*1502* is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of *HLA-B*1502* prior to initiating treatment with Tegretol [carbamazepine]. Patients testing positive for the allele should not be treated with Tegretol unless the benefit clearly outweighs the risk. Prior to initiating Tegretol therapy, testing for *HLA-B*1502* should be performed in patients with ancestry in populations in which *HLA-B*1502* may be present. (Revised 03/06/2013)
Chlordiazepoxide-amitriptyline	CYP2D6	Precautions	…PMs have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses…the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). (Revised 08/2007)
Clomipramine	CYP2D6	Drug Interactions	PMs have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). (Revised 10/26/2012)
Clozapine	CYP2D6	Drug Interactions, Clinical Pharmacology	CYP2D6…PM…individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. (Revised 03/22/2013)
Desipramine	CYP2D6	Drug Interactions	…PMs have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses…the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). (Revised 11/19/2012)
Dextromethorphan-quinidine	CYP2D6	Clinical Pharmacology, Warnings, Precautions, Drug Interactions	The quinidine component of NUEDEXTA [dextromethorphan-quinidine] is not expected to contribute to the effectiveness of NUEDEXTA in PMs, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with NUEDEXTA. (Revised 10/2010)
Doxepin	CYP2D6	Precautions	PMs of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.

Drug or Drug Combination	Pharmacogenomic Biomarker	Label Section	Label Information[23]
			(Revised 10/30/2011)
Fluoxetine	CYP2D6	Clinical Pharmacology, Warnings, Precautions	A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme CYP2D6…PM…these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. (Revised 01/30/2009)
Fluoxetine-olanzapine	CYP2D6	Clinical Pharmacology, Drug Interactions	Same as fluoxetine. (Revised 01/03/2013)
Fluvoxamine	CYP2D6	Drug Interactions	…an in vivo study of fluvoxamine single-dose pharmacokinetics in 13 PMs [CYP2D6] subjects demonstrated altered pharmacokinetic properties compared to 16 EMs: mean C_{max}, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. (Revised 11/30/2012)
Galantamine	CYP2D6	Special Populations	*O*-demethylation, mediated by CYP2D6 was greater in EMs of CYP2D6 than in PMs. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity. In studies of oral 3H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers. CYP2D6 PMs had drug exposures that were approximately 50% higher than for EMs. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 PMs demonstrated a similar C_{max} and about 35% AUC_{∞} increase of unchanged galantamine compared to EMs. Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in PMs compared to EMs. Dosage adjustment is not necessary in patients identified as PMs as the dose of drug is individually titrated to tolerability. (Revised 06/2013)
Iloperidone	CYP2D6	Clinical Pharmacology, Drug Interactions, Dosage and Administration, Specific Populations, Warnings, Precautions	FANAPT [iloperidone] dose should be reduced by one-half for PM of CYP2D6. The observed mean elimination half-lives for iloperidone, P88, and P95 in CYP2D6 EMs are 18, 26, and 23 hours, respectively, and in PMs are 33, 37, and 31 hours, respectively… The iloperidone metabolite P95 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for EM and 25% for PM. The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EMs and PMs, respectively…Laboratory tests are available to identify CYP2D6 PMs. (Revised 01/31/2013)
Imipramine	CYP2D6	Drug Interactions	PMs have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA). (Revised 10/26/2012)
Modafinil	CYP2D6	Drug Interactions	… In individuals deficient in the enzyme CYP2D6 … the levels of CYP2D6 substrates such as tricyclic antidepressants and selective serotonin reuptake inhibitors, which have ancillary routes of elimination through CYP2C19, may be increased by coadministration of modafinil. Dose adjustments may be necessary for patients being treated with these and similar medications.

Drug or Drug Combination	Pharmacogenomic Biomarker	Label Section	Label Information[23]
			(Revised 10/21/2010)
Nortriptyline	CYP2D6	Drug Interactions	…PMs have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). (Revised 10/26/2012)
Paroxetine	CYP2D6	Clinical Pharmacology, Drug Interactions	Included only information about inhibition of CYP2D6. (Revised 04/28/2011)
Phenytoin	*HLA-B*1502*	Warnings	Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of *HLA-B*1502*, an inherited allelic variant of the HLA-B gene, in patients using carbamazepine. Limited evidence suggests that *HLA−B*1502* may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for *HLA-B*1502*. (Revised 03/06/2013)
Perphenazine	CYP2D6	Clinical Pharmacology Drug Interactions	PMs of CYP2D6 will metabolize perphenazine more slowly and will experience higher concentrations compared with normal or EMs. (Revised 10/2011)
Pimozide	CYP2D6	Warnings, Precautions, Contraindications	Individuals with genetic variations resulting in PM…exhibit higher pimozide concentrations than EM. The time to achieve steady state pimozide concentrations is expected to be longer (approximately 2 weeks) in PM because of the prolonged half-life. Alternative dosing strategies are recommended in patients who are genetically PM. Children dosing: At doses above 0.05 mg/kg/day, CYP2D6 genotyping should be performed. In PM, ORAP [pimozide] doses should not exceed 0.05 mg/kg/day, and doses should not be increased earlier than 14 days. Adult dosing: At doses above 4 mg/day, CYP 2D6 genotyping should be performed. In PM, ORAP doses should not exceed 4 mg/day, and doses should not be increased earlier than 14 days. (Revised 09/27/2011)
Protriptyline	CYP2D6	Precautions	PMs have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. …the increase in plasma concentration may be small or quite large (8 fold increase in plasma AUC of the TCA). (Revised 03/2010)
Risperidone	CYP2D6	Clinical Pharmacology, Drug Interactions	EMs convert risperidone rapidly into 9-hydroxyrisperidone, whereas PMs convert it much more slowly. Although EMs have lower risperidone and higher 9-hydroxyrisperidone concentrations than PMs, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in EMs and PMs. (Revised 08/02/2012)
Tetrabenazine	CYP2D6	Dosage and Administration, Warnings, Clinical Pharmacology	Doses above 50 mg should not be given without CYP2D6 genotyping patients to determine if they are PM. …CYP2D6 testing is necessary to determine whether patients are PMs, EMs or IMs of XENAZINE [tetrabenazine]. Patients who are PMs of XENAZINE will

Drug or Drug Combination	Pharmacogenomic Biomarker	Label Section	Label Information[23]
			have substantially higher levels of the primary drug metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) than patients who are EMs. The dosage should be adjusted according to a patient's CYP2D6 metabolizer status. In patients who are identified as CYP2D6 PMs, the maximum recommended total daily dose is 50 mg and the maximum recommended single dose is 25 mg. Genotyped patients who are identified as EMs or IMs of CYP2D6, … The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg. (Revised 06/2011)
Thioridazine	CYP2D6	Precautions, Warnings, Contraindications	Reduced cytochrome CYP2D6 isozyme activity…would be expected to augment the prolongation of the QTc interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes type arrhythmias…thioridazine is contraindicated…who are known to have a genetic defect leading to reduced levels of activity of CYP2D6. (Revised 04/2011)
Trimipramine	CYP2D6	Drug Interactions	PMs have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). (Revised 12/03/2012)
Valproic Acid	Urea cycle disorders (NAGS, CPS1, ASS1, OTC, ASL, ARG)	Contraindications, Precautions, Adverse Reactions	Valproic acid is contraindicated in patients with known urea cycle disorders. Prior to the initiation of valproate therapy, evaluation for urea cycle disorders should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of urea cycle disorders or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of urea cycle disorders. (Revised 02/27/2013)
Venlafaxine	CYP2D6	Drug Interactions	In a clinical study involving PMs and EMs, the total concentration of active compounds (venlafaxine plus ODV), was similar in the two metabolizer groups. Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. (Revised 12/12/2012)

CYP = cytochrome P450; PM = poor metabolizer; EM = extensive metabolizer; IM = intermediate metabolizer; HLA = human leukocyte antigen; NAGS= N-acetylglutamate synthase; CPS1= carbamoyl phosphate synthase I; ASS1= argininosuccinate synthetase 1; OTC= ornithine carbamoyltransferase; ASL= argininosuccinate lyase; ARG = arginase.

*Pharmacogenomic information was included only in the label information for the diazepam rectal gel formulation, not the oral tablet.

Table 2

Pharmacogenomic Testing Resources for Variants Influencing Neuropsychiatric Medications

Pharmacogenomic Testing Resource	CYP2D6 Variants Assayed	CYP2C19 Variants Assayed	Other Genes Assayed
Testing services or laboratories and associated platforms and variants tested			
AssureRx (GeneSightRx)[53]	*1, *2, *2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41, Duplication	*1, *2, *3, *4, *5, *6, *7, *8	*SLC6A4, HTR2A*
Genelex (You Script)[54]	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41, Duplication	*1, *2, *3, *4, *5, *6, *7, *8, *17	*CYP2C9, VKORC1*
Genomas (HILOmet PhyzioTypeSystem)[55]	*1, *3, *4, *5, *6, *9, *10, *17, Duplication	*1,*2,*3	*CYP2C9*
Matrix Genomics[56]	PM, IM, EM, UM (variants not specified)	*2, *3, *4, *5, *6, *7, *8, *17	*VKORC1, CYP2C9, CYP4F2, GGCX, APOE*
LUMINEX xTAG CYP2D6[57]	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *29, *35, *41, Duplication	Not applicable	Not applicable
Mayo Clinic[58]	*1, *2,*2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14A, *14B, *15, *17, *41, Duplication	*1, *2, *3, *4, *6, *7, *8, *17	*CYP3A4, UGT1A1, TPMT, HTR2A, HTR2C CYP2C9, CYP1A2, VKORC1, DRD4, DRD3, HLAB*5801, HLAB*1502, HLAB*5701, SLC6A4 (5-HTTLPR)*
23 and Me[59]	Not available	*1, *2, *3, *4, *8, *17	*HLAB*5701, ALDH2, ABCB1, ADRB1, CYP1A2, DYPD, ITPA, OPRM1*, rs3129900 (intronic), *ATM, F5, ANKK1, BCHE, IL28B, GPC5, COQ2, TPMT, CYP2C9, VKORC1*
Quest Diagnostics[60]	Variants not specified	*1-*10, *12, *17	*CYP2C9, HLA-B*1502, TPMT, UGT1A1, LPA, KIF6, CYP3A4, CYP3A5, CYP2C9, APOE, VEGF*
Laboratory Corporation of America[61]	*1, *2, *3, *4. *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41, *1XN, *2XN, *4XN, *10XN, *17XN, *41XN.	*2, *3, *4, *5, *6, *8, *17	*CYP2C9, HLA-B*1502, VKORC1, TPMT, APOE, IL28B, UGT1A1, MTHFR*
Genomind[62]	Variants not specified	Variants not specified	*CYP2C9, 5-HTT, 5HT2C, DRD2, ANK3, CACNA1C, COMT, MTHFR*
PGxl[63, 64]	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41	Variants not specified	*CYP2C9, CYP1A2, NAT2, HLA-B*5701, 5-HTTLPR, MTHFR*
MyGene[65]	Variants not specified	Variants not specified	*CYP2C9*, Carbamazepine PGx (Variants not specified)
ARUP Laboratories[66]	*1, *2, *2A, *3, *4, *5, *6, *7, *8, *9, *10, *12, *14, *17, *29, *41	*2, *3, *4, *6, *7, *8, *9, *10, *17	*CYP2C9, MTHFR, TPMT*

Pharmacogenomic Testing Resource	CYP2D6 Variants Assayed	CYP2C19 Variants Assayed	Other Genes Assayed
Testing platforms that may be available in independent CLIA-certified clinical laboratories or research laboratories			
The AmpliChip CYP450 Test[67]	*1, *2, *2ABD,*3, *4ABDJK, *5, *6ABC, *7, *8, *9, *10AB, *11, *15, *17, *19, *20, *29, *35, *36, *40, *41,*1XN (Duplication), *2XN, *4XN, *10XN, *17XN, *35XN, *41XN	*1, *2, *3	NA
INFINITI (AutoGenomics)[68, 69]	*2, *3, *4, *5, *6, *7, *8, *9, *10, *12, *14, *17, *29, *41A, *XN (Duplication)	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *17	*APOE, CYP2C9, CYP3A4, CYP3A5, SULT1A1, ABCB1 (MDR1), DYPD, MTHFR, TYMS, UGT1A1, NAT2*
DMET Plus (Affymetrix)[70]	*3, *4, *5, *6, *7, *9, *11, *12, *14 or *8, *15, *18, *19, *20, *21, *29(2 SNPs), *38, *40, *41, *42, *44, *56, CYP2D6_4180G>C, CYP2D6_2850C>T, CYP2D6_1661G>C, CYP2D6_1023C>T, CYP2D6_100C>T, CYP2D6_-1584C>G, CYP2D6_-1770G>A, CYP2D6_-1961C>G>A, CYP2D6_-2178G>A	*2,*2B, *3, *4, *5, *6, *7, *8, *9, *10, *12, *13, *14, *15, *17, CYP2C19_721insG, CYP2C19_80161G>A, CYP2C19_90052delG	1,936 SNP, copy number, and indel markers across 231 genes assayed
VeraCode ADME Core Panel (Illumina)[71]	*2, *2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *18, *91, *20, *21, *38, *40, *41, *42, *44, *56	*2, *3, *4, *5, *6, *7, *8, *12, *17 (3 SNPhap)	*ABCB1, ABCC2, ABCG2, CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2E1, CYP3A4, CYP3A5, DPYD, GSTM1, GSTP1, GSTT1, NAT1, NAT2, SLC15A2 SLC22A1, SLC22A2, SLC22A6, SLCO1B1, SLCO1B3, SLCO2B1, SULT1A1, TPMT, UGT1A1, UGT2B15, UGT2B15, UGT2B17, UGT2B7, VKORC1*
iPlex ADME PGx Panel (Sequenom)[72]	*1A, (*2A;*31;*51), (*2L;*35;*71), *3, *4, *4M, *6, *7, *8, *9, (*10;*36;*37;*47;*49;*52;*54;*57;*65;*72), *11, *12, *14A, *14B, *15, *17, *18, *19, *20, *21A, *21B, *30, *38, *40, *41, *42, *44, *56A, *56B, *58,*64, *69 CNV Assay: *5, *NxN (Haplotypes are identified manually)	*1, (*1B;C;*9), *2, *3, *4, *5A, *5B, *6, *7, *8, *12, *17	*ABCB1, ABCC2, ABCG2, COMT, CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2E1, CYP3A4, CYP3A5, DPYD, GSTM1, GSTP1, GSTT1, GSTT2, NAT1, NAT2, SLC15A2 SLC22A1, SLC22A2, SLC22A6, SLCO1B1, SLCO1B3, SLCO2B1, SULT1A1, TPMT, UGT1A1, UGT2B15, UGT2B17, UGT2B7, VKORC1*
eSensor (GenMark Diagnostics, Inc.)[73]	Not applicable	*2, *3, *4, *5, *6, *7, *8, *9, *10, *13, *17	*CYP2C9, VKORC1*

CYP = cytochrome P450; PM = poor metabolizer; IM = intermediate metabolizer; EM = extensive metabolizer; UM = ultrarapid metabolizer.