Medical Policy Manual

**Topic:** Cytochrome p450 Genotyping

**Section:** Genetic Testing

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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

The purpose of *CYP450* genotyping is to tailor drug selection and dosing to individual patients based on their gene composition for drug metabolism. The goal of this testing is to lead to early selection and optimal dosing of the most effective drugs, while minimizing treatment failures or toxicities.

**Background**

Drug efficacy and toxicity vary substantially across individuals. Because drugs and doses are typically adjusted, if needed, by trial and error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Various factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation (polymorphisms) in genes coding for drug metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA polymorphisms (genotyping) in genes related to the metabolic pathway...
(pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse effects, and decrease medical costs.

**CYP450**

The cytochrome p450 family (CYP450) is a major subset of drug-metabolizing enzymes. The CYP450 family of enzymes includes but is not limited to:

- **CYP2D6** which metabolizes approximately 25% of all clinically used medications (e.g., dextromethorphan, beta-blockers, antiarrhythmics, antidepressants, and morphine derivatives), including many of the most prescribed drugs.
- **CYP2C19** which metabolizes several important types of drugs, including proton-pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline.

Some CYP450 genes are highly polymorphic, resulting in enzyme variants that may have variable drug-metabolizing capacities among individuals. The CYP450 metabolic capacities may be described as follows:

- **Extensive metabolizers (EM)**
  - Have two active CYP450 enzyme gene alleles, resulting in an active enzyme molecule
- **Poor metabolizers (PM)**
  - Lack active CYP450 enzyme gene alleles
  - May suffer more adverse events at usual doses of active drugs due to reduced metabolism and increased concentrations
  - May not respond to administered prodrugs that must be converted by CYP450 enzymes into active metabolites
- **Intermediate metabolizers (IM)**
  - Have one active and one inactive CYP450 enzyme gene allele
- **Ultrarapid metabolizers (UM)**
  - Have more than two active CYP450 gene alleles
  - May not reach therapeutic concentrations at usual, recommended doses of active drugs
  - May suffer adverse events from prodrugs that must be converted by CYP450 enzymes into active metabolites

It is important to note that many drugs are metabolized by more than one enzyme, either within or outside of the CYP450 family. Reduced activity in a particular CYP450 enzyme because of genotype may not affect outcomes when other metabolic pathways are available and when other confounders influence drug metabolism, such as interactions between different metabolizing genes, interactions of genes and environment, and interactions among different non-genetic factors.

**CYP450 Genotyping**

The purpose of CYP450 genotyping is to tailor drug selection and dosing to individual patients based on their gene composition for drug metabolism. In theory, this should lead to early selection and optimal dosing of the most effective drugs, while minimizing treatment failures or toxicities.

Diagnostic genotyping tests for certain CYP450 enzymes are now available:
The AmpliChip® (Roche Molecular Systems, Inc.) is an U.S. Food and Drug Administration (FDA)-approved, microarray-based pharmacogenomic test. The assay distinguishes 29 known polymorphisms in the CYP2D6 gene and two major polymorphisms in the CYP2C19 gene.[1]

The INFINITI CYP2C19 Assay (AutoGenomics, Inc.) was cleared for marketing in October 2010 based on substantial equivalence to the AmpliChip CYP450 test. It is designed to identify variants within the CYP2C19 gene (*2, *3, and *17).

The Spartan RX CYP2C19 Test System (Spartan Bioscience), designed to identify variants in the CYP2C19 gene (*2, *3, and *17 alleles), was cleared for marketing in August 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.

Verigene CYP2C19 Nucleic Acid Test (Nanosphere Inc.), designed to identify variants within the CYP2C19 gene, was cleared for marketing in November 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.

The xTAG® CYP2D6 Kit (Luminex Molecular Diagnostics) was cleared for marketing in August 2010 based on substantial equivalence to the AmpliChip CYP450 test. It is designed to identify a panel of nucleotide variants within the polymorphic CYP2D6 gene on chromosome 22.

The xTAG® CYP2C19 Kit v3 (Luminex Molecular Diagnostics), designed to identify variants in the CYP2C19 gene (*2, *3, and *17 alleles) was cleared for marketing in September 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.

Some tests are offered as in-house laboratory-developed test services. These tests do not require FDA approval.

Several manufacturers market panels of diagnostic genotyping tests for CYP450 genes, such as the YouScript Panel (Genelex Corp.), which includes CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP3A4 and CYP3A5. Other panel tests include both CYP450 genes and other non-CYP450 genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health Inc.); these tests are beyond the scope of this policy.

MEDICAL POLICY CRITERIA

I. CYP2C19 genotyping may be considered medically necessary for the following indications:

   A. To aid in the choice of clopidogrel (Plavix®) versus alternative anti-platelet agents; or
   B. To guide decisions on the optimal dosing for clopidogrel.

II. CYP2D6 genotyping to determine drug metabolizer status may be considered medically necessary for patients with:

   A. Gaucher disease type I being considered for treatment with eliglustat (Cerdelga™); or
   B. Huntington disease being considered for treatment with tetrabenazine (Xenazine®) in a dosage greater than 50mg per day.

III. Except as defined in Criteria I. or II. above, CYP450 (including CYP2C19, and CYP2D6 genotyping) is considered investigational for all indications, including but not limited to, medication selection and dose management for the following:

   A. Antipsychotics
B. Anti-tuberculosis medications
C. Atomoxetine HCl
D. Beta Blockers
E. Codeine
F. Efavirenz
G. H. pylori infection
H. Immunosuppressant for organ transplantation
I. Selective norepinephrine reuptake inhibitors
J. Selective serotonin reuptake inhibitor (SSRI)
K. Tamoxifen
L. Tricyclic antidepressants

IV. CYP2C9 and VKORC1 genotyping for the purpose of warfarin dose management, including use in guiding the initial warfarin dose, is considered investigational.

SCIENTIFIC EVIDENCE

Validation of genotyping to improve pharmacologic treatment outcomes is a multistep process. In general, major suggested steps in the validation process are as follows:

- Establish the specific genotyping test performance characteristics, i.e., does the test accurately and reproducibly detect the gene markers of interest (analytic validity).
- For each drug of interest, conduct preliminary performance study(ies) in relevant populations or population subsets as appropriate to evaluate the strength of the associations between the selected genetic markers and dose, therapeutic efficacy, and/or adverse events; may be retrospective (clinical validity).
- Conduct prospective trial(s) in relevant patient populations to compare the use of genotyping for specific genetic markers to guide prescribing and dosing to standard treatment without genotyping. Determine whether genotyping improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate (clinical utility).

The following limitations in the current evidence for therapeutic agents other than clopidogrel and eliglustat were noted:

- The available evidence is not sufficient to establish how CYP450 genotyping improves patient management with respect to drug selection and dosing compared to standard treatment without genotyping.
- It is not known if genotyping improves patient outcomes such as therapeutic effect, time to effective
dose, and adverse event rate.

- In general, most published CYP450 pharmacogenomic studies are retrospective evaluations of CYP450 genotype associations, reporting intermediate outcomes (e.g., circulating drug concentrations) or less often, final outcomes (e.g., adverse events or efficacy). Studies are mostly small and under-powered.
- There is a lack of randomized, prospective studies evaluating the clinical utility of CYP450 genotyping for any of the indications discussed below.

Antipsychotics Selection and Dosing

Because most patients with schizophrenia take combinations of psychoactive agents for extended periods of time, drug-drug and drug-environmental interactions may influence the CYP450 metabolic phenotype in addition to genotype. In addition, some antipsychotic medications are metabolized by multiple CYP450 enzymes and dominant pathways may vary. Several classical antipsychotic drugs inhibit the CYP450 enzyme required for their metabolism and may render the patient a phenotypic poor metabolizer despite an extensive metabolizer genotype. Thus, dosing algorithms need to accommodate both genetic influences and other interactions.

Literature Appraisal

Systematic Reviews and Meta-analysis

In a 2013 systematic review, the pharmacogenetics of risperidone was evaluated. The review identified 10 prospective nonrandomized, uncontrolled cohort studies, one retrospective cohort study, one prospective case-control study, and one retrospective case series. While there were trends toward increased adverse effects in poor metabolizers, most outcomes were not significant. Based on the results of the review, the authors concluded that routine genotyping should not be used for screening. Further, authors suggest that adequately powered clinical and epidemiologic studies are warranted to clarify the role of CYP2D6 genotyping in practice.

In 2011, Fleeman et al. published a systematic review and meta-analyses of CYP450 testing for use in prescribing antipsychotics in adults with schizophrenia. After conducting a search of 2841 publications, the authors identified 47 studies that described clinical validity, but failed to identify published studies on the clinical utility of testing. The authors found no convincing evidence of an association between test results and either drug efficacy or toxicity. When seen, differences were considered too small to be clinically meaningful (e.g., an association of mutation status with tardive dyskinesia).

Nonrandomized Studies

The evidence is limited to small, nonrandomized and retrospective studies of antipsychotics and CYP450 metabolism. No prospective trials of genotype-directed antipsychotic selection or dosing have been reported. Prospective randomized controlled clinical trials are needed to determine the independent contribution of CYP450 on both initial dosing and therapeutic drug monitoring.

Clinical Practice Guidelines

Currently no published clinical practice guidelines recommend CYP450 genetic testing for the selection and dosing of antipsychotics.
Individuals with genetic variants in the *CYP2D6* gene may be at increased risk for adverse effects of antipsychotic drugs, particularly extrapyramidal effects such as tardive dyskinesia and pimozide-induced arrhythmias. However, the clinical utility of testing is uncertain, since management changes as a result of genetic testing have not been evaluated.

**Anti-tuberculosis Medications**

**Literature Appraisal**

A number of studies have reported an association between *CYP2E1* status and the risk of liver toxicity from antituberculosis medications.

**Systematic Reviews**

In a meta-analysis published in 2014, Sheng and others investigated the potential association between cytochrome P450 2E1 (*CYP2E1*) polymorphisms and the risk of anti-tuberculosis drug-induced hepatotoxicity (ATDH).\[^1^\] Compared with the wild genotype (c1/c1), the odds ratio (OR) of ATDH was 1.41 (95% CI: 1.1-1.82, P=0.007) for the PstI/RsaI polymorphism, and 0.78 (95% CI: 0.51-1.18, P=0.23) for the DraI polymorphism. Compared with individuals with N-acetyltransferase 2 (NAT2) fast or intermediate acetylator genotype and c1/c1 genotype patients who were NAT2 slow acetylators and carried the high activity *CYP2E1* c1/c1 genotype had higher risk for ATDH (OR=3.10, P<0.0001). Authors concluded the meta-analysis indicated that the *CYP2E1* c1/c1 genotype may be a risk factor for ATDH.

A meta-analysis of available trials was reported by Deng et al. in 2013.\[^1^\] Compared with wild type genotype, patients with any variant genotype had an increased risk of liver toxicity (OR 1.36, 95% CI 1.09-1.69). Patients who were slow metabolizers had the highest risk of toxicity (OR 1.88, 95% CI 1.14-3.09), and this overall risk was also increased in Asian patients. This study does not address the question of whether genetic testing can reduce liver damage from anti-tuberculosis medications, compared to the usual strategy of monitoring liver enzymes and adjusting medications based on enzyme levels.

**Clinical Practice Guidelines**

Currently no published clinical practice guidelines recommend *CYP450* genotyping for the selection and dosing of anti-tuberculosis medications.

**Conclusions**

The clinical utility of testing for *CYP450* genotyping is uncertain, since management changes for antituberculosis medications based on genotyping results has not been evaluated.

**Beta Blocker Selection and Dosing**

**Literature Appraisal**

No prospective randomized controlled trials of genotype-directed beta blocker selection and dosing have
been reported.

**Nonrandomized Studies**

Existing studies have reported contradictory findings concerning the association of the CYP2D6 genotype and the response to beta blockers. A few studies have indicated that lipophilic beta selective adrenergic receptor antagonists, such as metoprolol used in treating hypertension, may exhibit impaired elimination in patients with CYP2D6 polymorphisms.\[13-17\] In addition, increased risk of bradycardia was observed in patients found to be poor metabolizers (CYP2D6 *4/*4), although the clinical significance of this observation remains to be defined.\[13,18\]

In contrast, it has also been reported that no difference in response to metoprolol or carvedilol was observed according to genotype.\[19,20\]

**Clinical Practice Guidelines**

There are currently no published clinical practice guidelines recommend CYP450 genotyping for the selection and dosing of beta-blocker medications.

**Conclusions**

CYP2D6 genetic variants may be associated with response to beta-blocker treatment, but little evidence currently exists on the clinical utility of testing for CYP2D6 variants in improving outcomes from beta-blocker treatment.

**Clopidogrel: Determining Risk of Atherothrombotic Events after an Acute Coronary Syndrome or a Percutaneous Coronary Intervention**

Dual antiplatelet therapy with aspirin and clopidogrel is currently recommended for the prevention of atherothrombotic events after acute myocardial infarction. However, a substantial number of subsequent ischemic events still occur, which may be at least partly due to interindividual variability in the response to clopidogrel. Clopidogrel, a prodrug, is converted by several CYP450 enzymes, including CYP2C19, to an active metabolite. However, variation in clopidogrel response is an extremely complicated process impacted by a wide range of both genetic and environmental factors, including patient compliance, metabolic state, and drug and food intake.

Prospective, randomized controlled clinical trials are needed to demonstrate the clinical utility of CYP450 testing in this patient population. Specifically, additional studies are needed that demonstrate reduced recurrence rates for carriers of CYP2C19 variants who are prospectively treated according to genotype.

**Literature Appraisal**

**Systematic Reviews**

Several systematic reviews and meta-analyses have been published, all suggesting that CYP2C19 gene polymorphisms do not have a substantial or consistent influence on the clinical efficacy of clopidogrel:
In 2015, Osnabrugge et al. reported a systematic review of 11 meta-analyses which summarized studies evaluating the associations between CYP2C19 genetic status and outcomes in clopidogrel-treated patients.\[^{21}\] The 11 meta-analyses included a total of 30 primary studies, but not all studies were included in all meta-analyses. Among the 30 primary studies, there were 23 cohort studies and seven post hoc analyses of RCTs. Eight out of 11 meta-analyses on clinical end points reported a statistically significant association between CYP2C19 genotype and outcomes, with mean effect sizes ranging from 1.26 to 1.96. Five of these eight concluded that there was an association between CYP2C19 Genotype and the clinical end point, two inferred that there was a possible association, and one concluded that the association was not proven because of publication bias. For the outcome of stent thrombosis, all 11 meta-analyses reported a statistically significant association between CYP2C19 genotype and stent thrombosis, with mean effect sizes ranging from 1.77 to 3.82.

In 2013, Mao et al. conducted a systematic review and meta-analysis of studies assessing the effect of CYP2C19 polymorphisms on clinical outcomes in patients with coronary artery disease treated with clopidogrel.\[^{22}\] The authors included 21 studies involving 23,035 patients, including prospective cohort studies and post-hoc analyses of RCTs involving patients with coronary artery disease. Carriers (N=6868) of the CYP2C19 variant allele had a higher risk of adverse clinical events than the 14,429 non-carriers (OR=1.50; 95% CI, 1.21 to 1.87; p<0.000). Patients with a loss-of-function CYP2C19 allele had a higher risk of MI (OR=1.62; 95% CI, 1.35 to 1.95; p<0.000) and a higher risk of in-stent thrombosis, among those who underwent stent implantation (OR=2.08; 95% CI, 1.67 to 2.60; p<0.000).

In 2011, Bauer et al. carried out an extensive literature review and meta-analysis of the genetic studies examining the impact of variants of the CYP2C19 genotype on the clinical efficacy of clopidogrel.\[^{23}\] Out of 4,203 identified publications, 15 studies met the prespecified inclusion criteria. When comparing carriers of at least one reduced function allele of CYP2C19 with non-carriers, the unadjusted odds ratios of major adverse events were higher in three studies, lower in one, and not significantly different in eight. For stent thrombosis the odds ratio associated with reduced function allele carrier status was reduced in four studies but showed no significant difference in five. No studies showed a significant positive or negative impact on outcomes as a result of CYP2C19*17 testing. The overall quality of evidence was graded as low. The authors concluded that “accumulated information from genetic association studies does not indicate a substantial or consistent influence of CYP2C19 gene polymorphisms on the clinical efficacy of clopidogrel. The current evidence does not support the use of individualized antiplatelet regimens guided by CYP2C19 genotype.”

Also in 2011, Holmes et al. searched PubMed and EMBASE for studies linking CYP2C19 testing to treatment with clopidogrel.\[^{24}\] They identified 32 studies including 42,106 participants. Twenty one studies included patients with acute coronary syndromes and eight studies included patients with stable coronary heart disease – the latter usually associated with coronary stent placement. While the authors observed a decrease in the measurable concentration of clopidogrel metabolite in patients with a loss-of-function gene on 75 mg of clopidogrel, they were unable to show that this resulted in a clinically meaningful change in outcomes. Of particular note was the observation that when studies were stratified by numbers of outcome events, there was a clear trend toward the null in larger studies, consistent with small-study bias. The strongest data supporting use of testing was in the prediction of stent thrombosis, with a risk ratio of 1.75 (CI 1.50 to 2.03) for fixed effects and 1.88 (CI 1.46 to 2.41) for random effects modeling. Assuming an event risk of 18 per 1000 in the control group they calculated that this corresponded to an absolute increase of 14 stent thromboses per 1000 patients. Holmes et al. noted a trade-off between decreased risk of bleeding with loss of function that in part appeared to mitigate increased susceptibility to thrombosis. They cautioned that efforts to personalize treatment in the loss-
of-function setting should be considered carefully because efforts to improve efficacy might be offset by risks of harms such as bleeding.

In a related editorial, Beitelshees noted that the results of the Holmes et al. analysis may have been compromised by the fact that patients who did not undergo percutaneous coronary intervention (PCI) were included.[25] They concluded that the association between CYP2C19 genotype and adverse outcomes with clopidogrel treatment may not be present in all settings and may be strongest for clopidogrel indications with the greatest effects such as patients undergoing PCI. This observation is supported by observations in the CHARISMA genetics study reported by Bhatt.[26] A total of 4819 patients were genotyped in this study and no relationship between CYP2C19 status and ischemic outcomes in stable patients was observed. Bhatt also observed significantly less bleeding in this subgroup.

**Randomized Controlled Trials (RCTs)**

Roberts et al. reported on the use of a point-of-care CYP2C19*C genetic test for treatment selection (standard treatment [prasugrel] versus clopidogrel).[27] In this controlled trial, patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome or stable angina were randomized to genotyping for treatment selection or standard treatment. In the tested group, carriers were given 10 mg of prasugrel daily. Non carriers and all patients in the control group were given 75 mg of clopidogrel per day. The primary endpoint was high on-treatment platelet reactivity as the primary endpoint. This measure is used as a marker of cardiovascular events. In the group with genotyping none of the 23 carriers had high on-treatment platelet reactivity; in the group receiving standard treatment 30% of 23 carriers had high on-treatment platelet reactivity. These authors concluded that rapid genotyping with subsequent personalized treatment reduces the number of carriers treated who exhibit high on-treatment reactivity. The authors do note that alternative approaches using either phenotyping or a combination of both phenotyping and genotyping might optimize treatment decision making.

Mega et al. also reported on the use of CYP2C19 genotyping for dosing of clopidogrel and the effect on platelet reactivity in patients with stable cardiovascular disease.[28] Their findings suggest that changes in platelet reactivity in carriers may be dose dependent and that in PCI patients heterozygous carriers might require up to triple dosing of clopidogrel to reach a desired target platelet reactivity level. In homozygous carriers, even with higher clopidogrel doses, platelet reactivity cannot be raised to the level of clopidogrel treatment in non-carriers.

**Nonrandomized Studies**

Nonrandomized studies have reported conflicting findings. Several nonrandomized studies found increased risks of thrombotic events in patients treated with clopidogrel who were CYP2C19 variant carriers.[29-36] However, in one large retrospective study of 5,059 patients from two large RCTs that compared clopidogrel with placebo in reducing the rate of cardiovascular events, the authors reported that that the efficacy and safety of clopidogrel as compared with placebo was not affected by CYP2C19 loss of function alleles. Even when data were restricted to evaluation of patients homozygous for loss of function, no increased risk of cardiovascular events was observed.

Recent studies have suggested that changes in platelet reactivity in carriers may be dose-dependent and that in PCI patients, heterozygous carriers might require up to triple dosing of clopidogrel to reach a desired target platelet reactivity level.[28,37] In homozygous carriers, it has been reported that even with higher clopidogrel doses, platelet reactivity cannot be raised to the level of clopidogrel treatment in
non-carriers. In these patients other drugs such as prasugrel or ticagrelor may be used as treatment alternatives.

Desai et al. reported results of a study of antiplatelet therapy prescribing behavior for antiplatelet therapy for 499 patients with a recent acute coronary syndrome or percutaneous coronary intervention who underwent CYP2C19 genotyping.[38] Among the 146 subjects (30%) with at least 1 CYP2C19 reduced function allele, although providers were more likely to increase antiplatelet therapy intensification than for noncarriers, only 20% had their clopidogrel dose changed or were switched to prasugrel.

**U.S. Food and Drug Administration (FDA) Safety Communication**

In 2010, the FDA issued a public safety communication and added a boxed warning to the label of Plavix about the availability of genetic testing and alternative drug therapies in patients who are found to be poor metabolizers of the drug (patients with CYP2C19 *2/2, *3/3, or *2/3 genotypes). The FDA endorsement is based on retrospective analyses which suggested that PM status had a higher rate of cardiovascular events or stent thrombosis compared to EM.[37,39]

**Clinical Practice Guidelines**

A consensus statement by the American College of Cardiology (ACCF) foundation and the American Heart Association (AHA) on genetic testing for selection and dosing of clopidogrel was published in 2010.[40] The recommendations for practice included the following statements:

- Adherence to existing ACCF/AHA guidelines for the use of antiplatelet therapy should remain the foundation for therapy. Careful clinical judgment is required to assess the importance of the variability in response to clopidogrel for an individual patient and its associated risk to the patient.
- Clinicians must be aware that genetic variability in CYP enzymes alters clopidogrel metabolism, which in turn can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel has been associated with adverse patient outcomes in registry experiences and clinical trials.
- The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined.
- Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies. Both the selection of the specific test and the issue of reimbursement are important additional considerations.
- The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.
- There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance.

**Conclusions**

Individuals with genetic variants of cytochrome p450 have a decreased ability to metabolize clopidogrel, but the impact on clinically meaningful outcomes is uncertain. Despite this lack of evidence, FDA labeling recommends cytochrome p450 genetic testing for selection and dosing of clopidogrel (Plavix®).
Selection or Dosing of Codeine

Codeine is metabolized by CYP2D6 to morphine. Enhanced CYP2D6 activity (i.e., in CYP2D6 ultra-rapid metabolizers) predisposes to opioid intoxication.

Literature Appraisal

U.S. Food and Drug Administration (FDA) Safety Communication

In 2013, in response to reports of deaths that have occurred in children with obstructive sleep apnea who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being UMls of codeine due to a cytochrome CYP2D6 polymorphism, FDA added a black box warning to the labeling for codeine listing its use for postoperative pain management in children following tonsillectomy and/or adenoidectomy as a contraindication. The FDA’s guidelines state, “Routine CYP2D6 genotype testing is not being recommended for use in this setting because patients with normal metabolism may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers.”[41]

In 2007, the U.S. Food and Drug Administration (FDA) issued a warning regarding codeine use by nursing mothers. Nursing infants “may be at increased risk of morphine overdose if their mothers are taking codeine and are ultra-rapid metabolizers of codeine.” However, the FDA is not recommending genotyping for any population prior to prescribing codeine because “there is only limited information about using this test for codeine metabolism.”[29]

Clinical Practice Guidelines

Currently no published clinical practice guidelines recommend CYP450 genotyping for the selection and dosing of codeine for nursing mothers.

Conclusions

Enhanced CYP2D6 activity is associated with risk of accelerated codeine metabolism with high levels of circulating morphine in rapid metabolizers, which is thought to have contributed to deaths in infants of nursing mothers prescribed codeine and in pediatric patients post-tonsillectomy. The clinical utility of testing for CYP450 genotyping is uncertain, since management changes for codeine for nursing mothers based on genotyping results has not been evaluated.

Dose and Selection of Highly Active Antiretroviral Agents

Efavirenz

Current guidelines recommend efavirenz as a preferred non-nucleoside reverse transcriptase inhibitor component of highly active antiretroviral therapy for HIV-infected patients. Forty to 70% of patients report adverse central nervous system effects. While most resolve in the first few weeks of treatment, about 6% of patients discontinue efavirenz due to adverse effects.[42] Efavirenz is primarily metabolized by CYP2B6, and inactivating polymorphisms are associated with higher efavirenz exposure, although plasma levels appear not to correlate with side effects.

Randomized Controlled Trials
No randomized prospective trials of genotype-directed efavirenz dosing for the treatment of HIV infection have been reported.

**Nonrandomized Studies**

Limited reports suggest that CYP2B6 poor metabolizers have markedly reduced side effects while maintaining viral immunosuppression at substantially lower doses.[43,44] Simulations of such dose adjustments support this position.[45] Additional studies also report an association between polymorphism in CYP2B6 gene and early discontinuation of efavirenz treatment. However, further research is needed in order to examine the clinical utility of the observed association.

Cabrera et al. reported on an evaluation in 32 patients of the relationship between CYP2B6 polymorphisms and efavirenz clearance.[46] Although they reported that CYP2B6 polymorphisms could be used to account for only 27% of interindividual variability, they noted decreased clearance of 50% in the patient group with the G/T genotype and 75% with the T/T genotype. Based on this observation, they suggested a gradual reduction in dose of efavirenz be considered in patients with these phenotypes. They proposed use of a model to incorporate factors that affect drug levels. However, based on the complexity of factors involved in dosing, they concluded drug treatment should be carefully evaluated using therapeutic drug monitoring and assessment of clinical efficacy.

Two studies have been published, one evaluating 373 patients for polymorphisms in CYP2B6 and constitutive androstane receptor (CAR)[1], and one evaluating genotyping for 23 markers in 15 genes[39]. Both demonstrated an association between markers and early efavirenz discontinuation. Both articles recommended further study to determine the clinical utility of these associations.

Lee et al. evaluated the effect of CYP2B6 G516T polymorphisms on the plasma efavirenz concentrations in HIV-infected patients, with or without concomitant rifampicin use.[47] The study included 171 HIV-infected patients including 18 with tuberculosis, 113 (66.1%) with CYP2B6 G516G, 55 (32.2%) with GT, and 3 (1.8%) with TT genotype. Patients with GT or TT genotype had a significantly higher plasma efavirenz concentration than those with GG genotype (2.50 vs 3.47 mg/L for GT genotype and 8.78 mg/L for TT genotype; p<0.001).

Bienvenu et al. evaluated the effect of single nucleotide polymorphisms (SNPs) in 5 drug metabolizing enzymes on plasma efavirenz levels and treatment response in patients treated with efavirenz alone (N=28) and when treated with cotreated with efavirenz and rifampicin-based TB treatment (N=62).[48] Serum efavirenz levels differed based on CYP1A2 genotype (T/G vs T/T) when patients were cotreated with efavirenz and rifampicin, but not when patients received efavirenz alone. High serum efavirenz levels were associated with CYP2B6 516T/T genotype, both with and without rifampicin treatment. CYP2B6 516T/T and 983T/T genotypes predicted supratherapeutic efavirenz levels (positive predictive value, 100%), particularly in the absence of rifampicin.

**Other Antiretroviral Therapies**

While the preponderance of the evidence related to CYP450 genetic testing for antiretroviral therapies has focused on efavirenz, there has been some investigation of pharmacogenomics testing for other antiretroviral therapies.

In a case-control analysis of 27 patients with nevirapine-induced Stevens-Johnson syndrome (SJS) induced by the non-nucleoside reverse transcriptase inhibitor nevirapine and 78 controls, Ciccacci et al.
found that polymorphisms in \textit{CYP2B6}, but not in \textit{CYP3A4} and \textit{CYP3A5}, were associated with SJS risk.\[49\] Additionally, in a prospective cohort study including 66 women receiving nevirapine, Oluka et al. reported that \textit{CYP2B6} genotype was associated with serum nevirapine concentration and CD4 counts.\[50\] Finally, Lu et al. reported that \textit{CYP3A5} polymorphisms are associated with serum concentrations of maraviroc, a CCR5 receptor antagonist used for HIV treatment, in healthy control subjects.\[51\]

**Clinical Practice Guidelines**

There are currently no published clinical practice guidelines recommend \textit{CYP450} genotyping for the dosing of efavirenz.

**Conclusion**

Genetic variants in \textit{CYP2B6} are associated with increased side effects for patients treated with efavirenz, leading to some recommendations to reduce dosing based on genotype results. The impact of this strategy on health outcomes has yet to be evaluated; therefore the clinical utility of genotyping for efavirenz dose is uncertain. Preliminary evidence suggests that \textit{CYP450} polymorphisms may be associated with serum levels and adverse effects of other antiretroviral therapies, but the clinical utility of these findings is also uncertain.

**Eliglustat (Cerdelga™) for Gaucher disease type I.**

Eliglustat (Cerdelga™), a small-molecule oral glucosylceramide analogue that inhibits the enzyme glucosylceramide synthase was developed by Genzyme for the treatment of Gaucher disease type 1 in adults.\[52\] Inhibition of this enzyme reduces the accumulation of the lipid glucosylceramide in the liver, spleen, bone marrow and other organs. Eliglustat is primarily metabolized by \textit{CYP2D6} and, therefore, \textit{CYP2D6} genotype/phenotype greatly impacts the dosing of eliglustat. A small number of adult patients who metabolize eliglustat more quickly or at an undetermined rate, based on \textit{CYP2D6} genotype, will not be eligible for eliglustat treatment.

**Literature appraisal**

There are no published studies that demonstrate how genotyping results for \textit{CYP2D6} affect selection and dosing for eliglustat (Cerdelga™).

**U.S Food and Drug Administration (FDA) Safety Communication**

In 2014, the U.S. Food and Drug Administration (FDA) labeling for eliglustat (Cerdelga™) included information on personalizing initial selection and dose according to genotyping results for \textit{CYP2D6}. The FDA labeling requires that patients be selected on the basis of \textit{CYP2D6} metabolizer status as determined by genotype, with recommendations based on genotype about dosage and concomitant use of \textit{CYP2D6} and \textit{CYP3A} inhibitors.\[53\]

**Clinical Practice Guidelines**

Currently no published clinical practice guidelines recommend CYP2D 6genotyping for the dosing of eliglustat.
Conclusions

Individuals with genetic variants of CYP450 have an increased ability to metabolize eliglustat, a small-molecule oral glucosylceramide analogue that inhibits the enzyme glucosylceramide synthase was for the treatment of Gaucher disease type 1. Although the current evidence is limited to industry-sponsored nonrandomized studies on the efficacy of eliglustat, FDA labeling recommends cytochrome p450 genetic testing for selection and dosing of eliglustat. Therefore, CYP450 genotyping may be considered medically necessary to guide selection and dose management of eliglustat.

H. pylori Infection

Currently, multiple regimens are available for treating H. pylori infection. These include proton pump inhibitors (PPI) to suppress acid production, in combination with antibiotic treatment, consisting of one or more agents such as amoxicillin, clarithromycin, or metronidazole. Genetic factors may influence the success of H. pylori treatment through effects on PPI metabolism. Individuals with polymorphisms in the CYP2C19 gene, a member of the cytochrome P450 (CYP450) family, metabolize PPIs more slowly than normal. Observational research suggests that patients who are extensive metabolizers of PPIs have lower eradication rates following standard treatment for H. pylori, compared with poor metabolizers.

If CYP2C19 status is known prior to treatment, adjustments could potentially be made in the selection of PPI and/or the dosing schedule to achieve optimal acid suppression in all patients. Improved eradication rates for H. pylori could lead to improved health outcomes by reducing the need for re-treatment following treatment failure, reducing recurrences of H. pylori-associated disorders, and reducing the morbidity and mortality associated with disease recurrence.

To determine whether treatment decisions based on genetic testing improve health outcomes, direct comparisons with standard treatment selection strategies are needed. Prospective randomized controlled trials (RCTs) comparing the two strategies are necessary for reliable comparisons. The optimal trial would isolate the impact of treatment changes made as a result of genetic status, be performed in the U.S. in a population with rates of CYP2C19 polymorphisms approximating that of the general U.S. population, use an approach to diagnosing H. pylori that reflects usual care in the U.S., and would use a standard treatment regimen recommended for U.S. patients.[54]

Literature Appraisal

Systematic Reviews

In 2013, Tang et al. published results from a meta-analysis of RCTs to re-evaluate the impact of CYP2C19 variants on PPI-based triple therapy for H. pylori infection.[55] Authors identified 16 RCT datasets derived from 3680 patients. There were significant differences in that rate between homozygous (HomEMs) and heterozygous (HetEMs) extensive metabolizers (OR 0.724; 95% CI 0.594-0.881), between HomEMs and poor metabolizers (PM) (OR 0.507; 95%CI 0.379-0.679), or between HetEMs and PMs (OR 0.688; 95%CI 0.515-0.920), regardless of the PPI being taken. Furthermore, sub-analysis of individual PPIs was carried out to explore the difference across all the PPIs used. A significantly low rate was seen in HomEMs vs. HetEMs taking either omeprazole (OR 0.329; 95%CI 0.195-0.553) or lansoprazole (OR 0.692; 95%CI 0.485-0.988), and also in HomEMs vs. PMs for omeprazole (OR 0.232; 95%CI 0.105-0.515) or lansoprazole (OR 0.441; 95%CI 0.252-0.771). However, there was no significant difference between HetEMs and PMs taking either one. No significant differences were observed for rabeprazole or esomeprazole across the CYP2C19 genotypes of interest. Authors concluded
that carriage of CYP2C19 loss-of-function variants is associated with increased H. pylori eradication rate in patients taking PPI-based triple therapies when omeprazole or lansoprazole is chosen. In the meta-analysis, individual PPIs were pooled without considering the dose, duration of therapy and the type of antibiotic agents, resulting in some confounders for CYP2C19 phenotypes and the eradication rates of PPI-based therapy. Therefore, results may not be generalizable to clinical practice.

**Randomized Controlled Trials (RCTs)**

A randomized, controlled trial comparing a pharmacogenomics-based treatment regimen with a standard regimen was evaluated.\cite{56} This study randomized 300 Japanese patients to a pharmacogenomics-based treatment regimen versus a standard treatment regimen. The TEC Assessment offered the following observations and conclusions concerning this study:

Eradication rates after first-line treatment were higher in this study for the pharmacogenomics group compared with the standard treatment group. However, because of numerous variations in treatment protocol within the pharmacogenomics group, it was not possible to determine whether the improvement resulted from the tailored PPI dosages according to CYP2C19 genetic status, or due to other variations in the treatment protocol unrelated to CYP2C19 status.

There were numerous variations in the treatment regimen within the experimental group that made it difficult to determine which specific aspects of the treatment regimen may have led to benefit. In particular, it appeared that clarithromycin resistance was an important factor in treatment success, and that there may have been an interaction between clarithromycin resistance and CYP2C19 status. From the data reported in the study, it was not possible to separate the potential impact of clarithromycin resistance on eradication rates from the impact of pharmacogenetically tailored PPI dosage schedules.

In addition to the limitations on internal validity, the clinical relevance of the study was also limited for several reasons. The treatment approach used was relatively intensive, including genetic testing for CYP2C19, esophagogastroduodenoscopy with biopsy for all patients, and testing of H. pylori isolates for clarithromycin resistance. This treatment approach was much more intensive than that generally used in the United States, where the diagnosis of H. pylori is usually made by noninvasive methods, and initial empiric treatment is instituted without isolating H. pylori or testing for resistance. Furthermore, the patient population was from Japan, limiting the generalizability of the results, especially given the ethnic differences in CYP2C19 genetic status.

Additional RCTs evaluating H. pylori eradication rates for different treatment regimens reported that the CYP2C19 genotype appears to play a role in eradication rates.\cite{57,58} However, these trials were not designed to compare a pharmacogenomics-based treatment regimen with a standard regimen.

**Nonrandomized Studies**

Additional small, nonrandomized and retrospective studies of CYP2C19 gene polymorphisms and H. pylori treatment have been published; however, the clinical utility of genotyping was not addressed.\cite{57,59-70}

**Clinical Practice Guidelines**

No evidence-based clinical practice guidelines were identified that recommend CYP450 (i.e., CYP2C19) genotyping to select and dose treatment for H. pylori eradication.
Conclusions

The clinical utility of testing for CYP450 genotyping is uncertain, since management changes to select and dose treatment for H. pylori eradication based on genotyping results has not been evaluated.

Immunosuppressant Dosing for Organ Transplantation

Immunosuppressive drugs administered to organ transplant patients have a narrow therapeutic index with the consequences of rejection or toxicity on either side. In addition, there is variability in patient response, requiring close clinical follow-up and routine therapeutic drug monitoring to maintain safety and efficacy. CYP3A5 genetic polymorphisms have been evaluated in relation to metabolism of immunosuppressant drugs.

Literature Appraisal

- Tacrolimus blood levels are related to CYP3A5 genetic variants, with an approximately 2.3-fold difference in daily dose required to maintain target concentration between CYP3A5*3 and CYP3A5*1 homozygous variants.[71]

- CYP3A5*1 carriers have been reported to have a significant delay in reaching target tacrolimus concentrations compared to non-carriers. Although the overall rate of acute rejection episodes was not higher in CYP3A5*1 carriers, their rejection episodes did occur earlier.[72]

- Population-based pharmacokinetic models for clearance of tacrolimus in kidney transplant recipients have been developed for both adult and children.[73,74] These models predict clearance based on CYP3A5*3/*3 as well as clinical factors. Results show that oral clearance of tacrolimus is impacted by body weight, hematocrit and time since transplant, in addition to CYP3A5*3/*3 polymorphisms.

- Pharmacogenetic applications for other immunosuppressants (sirolimus and cyclosporine) have also been investigated; however, evidence for clinical utility of genotyping for dosing of these drugs is even less clear than for tacrolimus. Thirty-seven studies were included in the

Systematic Review

In 2015, Rojas et al. published results from a systematic review and meta-analysis evaluating the effect of the CYP3A5 polymorphism on kidney transplant recipients treated with tacrolimus. The authors found that CYP3A5*1 carriers had significantly lower plasma tacrolimus concentration per daily dose per body weight than carriers of the CYP3A5*3/*3 genotype.[75] It is important to note that this review only included observational studies thereby precluding firm conclusions.

In a 2013 meta-analysis, Rojas and others investigated the effect of the CYP3A5 6986A>G polymorphism in liver donors and transplant recipients on tacrolimus pharmacokinetics.[76] The meta-analysis demonstrated the trough blood concentration normalized for the daily dose (C) per kilogram body weight (D) (C/D, ng/ml/mg/kg/day) ratio to be significantly higher in recipients with non-expressed donor variants at all time points. In recipients, the variant did not influence the C/D ratio. The authors concluded the presence of the CYP3A5 6986A>G polymorphism in the donor affects tacrolimus pharmacokinetics in the recipient for the first month after transplantation. Authors note the evidence
provided shows no effect of the recipient genotype; however, the quality of the evidence was low, thereby precluding the drawing of firm conclusions.

Buendia et al. used a random effects model to conduct a meta-analysis comparing tacrolimus daily dose, trough concentrations, and dose-adjusted trough concentrations across liver transplant donor and recipient genotype pairs. Eight studies (N=694) met inclusion criteria. Significantly lower tacrolimus trough concentrations were found when either the donor or recipient expressed a *1 allele up to 12 months post-transplant, requiring higher daily dose to maintain target drug concentrations.

**Randomized Controlled Trials**

Based on observations that patients with genetic variants of \( CYP3A5 \) require higher tacrolimus doses to achieve a therapeutic trough concentration (C0), Thervet et al. conducted an RCT to compare the proportion of tacrolimus-treated renal transplant patients within a targeted C0 range for 2 tacrolimus dosing strategies, \( CYP3A5 \) genotype-informed dosing or standard dosing. The study included 280 patients, 140 who received standard dosing and 140 who received \( CYP3A5 \) genotype-specific dosing. The genotype-directed therapy group was more likely to achieve the study’s primary outcome, proportion of patients with tacrolimus C0 in the target range after 6 oral doses, than the control group (43.2% [95% CI, 36% to 51.2%] vs 29.1% [95% CI, 22.8% to 35.5%]; p=0.030). The genotype-directed therapy group had fewer dose adaptations (281 vs 420; p=0.004). Graft function and survival were similar between groups.

**Nonrandomized Studies**

Passey et al used tacrolimus blood trough and dose information from 681 kidney transplant recipients to develop a predictive tool for tacrolimus apparent clearance, from which individual tacrolimus dosing could be extrapolated. The study’s final model included \( CYP3A5 \) genotype, along with other clinical factors, but was not validated in an independent population.

In a subsequent study, Boughton et al evaluated the previously-developed model in a single-center cohort of renal transplant recipients. The study found a weak correlation \((R=0.431)\) between clearance based on dose-normalized tacrolimus trough concentrations and the algorithm-predicted clearance.

Tapirdamaz et al. studied the influence of SNPs in the genes of donor and recipient calcineurin inhibitor (CNI) enzyme \( CYP3A5 \) and the CNI-transporting \( ABCB1 \) on the development of chronic kidney disease (CKD) following liver transplantation (LT). Tacrolimus predose concentrations and \( CYP3A5 \) 6986A>G and \( ABCB1 \) 3435C>T SNPs were determined in 125 LT recipients and their donors. Median follow-up was 5.7 years. CKD developed in 47 patients (36%). No correlation was found between CKD and tacrolimus levels or the investigated SNPs.

In 410 living-donor LT patients, Uesugi et al. found no significant effect of CyP3A5 genotype on the rate of acute cellular rejection between postoperative days 14 and 23. However, higher rates of acute cellular rejection were found in patients who received a graft liver with \( CYP3A5*1 \) allele than those with graft liver with the \( CYP3A5*3/*3 \) genotype.

**Clinical Practice Guidelines**

Currently no published clinical practice guidelines recommend \( CYP450 \) genotyping for the dosing of immunosuppressant medications.
Conclusions

*CYP3A5* genetic variants may be used to predict tacrolimus clearance. One RCT demonstrated that the use of a *CYP3A5* genotype-directed algorithm was associated with improvements in the proportion of patients with target tacrolimus concentration ranges. No differences in morbidity or mortality or graft survival were reported, which the authors attribute to a patient population at low risk of acute rejection or other clinical events. Additional studies of the clinical utility of *CYP3A5* genetic testing-based algorithms in tacrolimus management are needed. There is limited evidence on the impact of genotype on dosing on immunosuppressant medications.

Selective Norepinephrine Reuptake Inhibitors

**Antidepressants**

Selective norepinephrine reuptake inhibitors (SNRIs) are used most commonly as antidepressants. Available agents in the US include venlafaxine, duloxetine, and nefazodone. All of these drugs are metabolized by the cytochrome p450 system, and medication levels vary according to cytochrome p450 status.[83] Some of these agents, for example venlafaxine, are metabolized to an active metabolite by the *CYP2D6* enzyme, and other agents such as duloxetine are inhibitors of cytochrome p450 activity.

Lobello et al. tested patients from four RCTs of venlafaxine versus placebo for *CYP2D6* status and correlated genetic status, defined as either extensive metabolizers (EM) or poor metabolizers (PM), with response to treatment.[84] There were no significant differences in dose of the drug according to genetic status. In four of five comparisons, patients who were EMs had a better response to treatment as determined by depression rating scales. There was also a significantly greater percent of responders in the EM group compared to the PM. There were no differences in discontinuation of therapy or adverse event rates between the EM and PM group.

Waade et al. retrospectively evaluated the association between age, serum levels of venlafaxine and the SSRI escitalopram for different *CYP2D6* and *CYP2C19* genotype subgroups.[85] The study included 462 serum concentration measurements from 255 patients treated with venlafaxine and 953 serum concentration measurements from 541 patients treated with escitalopram. Patients were divided into three *CYP2D6* (venlafaxine) or *CYP2C19* (escitalopram) phenotype subgroups according to inherited genotype (PMs, heterozygous extensive metabolizers [HEMs], and EMs). An age-related difference (comparing patients <40 years, 40-65 years, and >65 years) was seen for venlafaxine, with a higher mean dose-adjusted serum concentration of venlafaxine for patients older than 65 years compared with those younger than 40 years in the PM group: 18.8 versus 2.4 (p<0.001). There were no significant age-related differences in serum venlafaxine concentration for HEM and EM patients and no association between age and escitalopram concentration regardless of genotype.

For duloxetine, the inhibitory effects on cytochrome p450 activity are manifested by higher drug concentrations for other medications metabolized by cytochrome p450 such as tricyclic antidepressants and/or SSRIs. Similarly, other inhibitors of cytochrome p450 such as paroxetine will increase levels of duloxetine.[86]

**Atomoxetine HCl Dosing For the Treatment of Attention-Deficit/Hyperactivity Disorder**
Atomoxetine HCl is a selective norepinephrine reuptake inhibitor that is prescribed to treat attention-deficit/hyperactivity disorder (ADHD). Atomoxetine HCl is primarily metabolized by CYP2D6.

The therapeutic window for atomoxetine is wide, and dosing is weight-based, initiated at a standard dose per kg and adjusted thereafter according to clinical response and adverse effects. At steady state dosing, CYP2D6 poor metabolizers have substantially higher atomoxetine plasma concentrations than normal, extensive metabolizers (EMs). However, because the drug is generally well tolerated across a wide range, adverse effects do not appear to be significantly associated with poor metabolizers.\[87,88\] After titration, mean doses for EMs and poor metabolizers also do not differ significantly.\[88,89\] However, more EM patients discontinued in one trial due to lack of efficacy\[89\] and poor metabolizers improved inattention scores more than EMs in another,\[88\] perhaps suggesting a need to re-examine recommended dosing limits.

The FDA decided not to include a recommendation to perform genotyping prior to prescribing atomoxetine. Dosing directions recommend a low starting dose to be increased to the target dose if well tolerated. Thus, genotyping for CYP2D6 poor metabolizers of atomoxetine is not recommended because the margin of safety is not exceeded and evidence to support guidelines for dosing such that patient outcomes are improved has not been collected.\[27,90,91\]

No randomized prospective trials of genotype-directed atomoxetine HCl dosing for the treatment of ADHD have been reported.

**Nonrandomized Studies**

Ramoz et al. recently reported on two independent cohorts of 160 and 105 ADHD children treated for six weeks with atomoxetine.\[91\] Interindividual response to the drug appeared independent of the genetic variants of CYP2D6. The authors did observe drug treatment and genomic associations, but these were found between drug response and a haplotype of the norepinephrine transporter (NET) gene–Slc6a2. It was suggested further study be applied to assessment of this region to better manage patients being treated with this drug.

In 2010, ter Laak et al. evaluated 100 patients treated for ADHD with standard doses of atomoxetine.\[92\] A neurologist identified 10 of these who, based on late response or adverse effects, were subject to CYP P450 testing. Eight of the 10 were found to have a nonfunctional or less functional 2D6 allele. Four of these children showed improved responses on decreased atomoxetine; four were taken off treatment because of initial adverse events. While it is plausible that pretreatment testing could yield improved results, the study was not designed to evaluate the actual effect of testing on treatment outcomes.

**Clinical Practice Guidelines**

Currently no published clinical practice guidelines recommend CYP450 genotyping for the selection and dosing of venlafaxine or other SNRIs.

**Conclusions**

SNRI metabolism is affected by genetic status of cytochrome p450, with the greatest potential clinical effect seen for venlafaxine. For this agent, EMs of CYP2D6 exhibit higher levels of the active metabolite and genetic status may have an impact on treatment response. A post-hoc re-analysis of data from multiple RCTs has correlated treatment response to venlafaxine with genetic status. No studies
have yet established that outcomes are improved as a result of genetic testing prior to initiating
venlafaxine or other SNRIs.

Atomoxetine is a SNRI that is used for ADD. It has a narrow therapeutic window, and there is potential
for PMs to reach serum levels that may be toxic. However, current recommendations for starting
atomoxetine at a low dose and watching closely for adverse effects while titrating higher should
minimize the risk of toxicity for PMs.

**Selective Serotonin Reuptake Inhibitors (SSRIs) Selection and Dosing**

*CYP2D6* and *CYP2C19* are the primary *CYP450* enzymes involved in the metabolism of SSRIs.

**Literature Appraisal**

**Systematic Reviews**

The Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC)
systematically reviewed the evidence on *CYP450* testing for adults treated with SSRIs for nonpsychotic
depression.[93] The report concluded, “The data fail to support a clear correlation between CYP
polymorphisms and SSRI levels, SSRI efficacy, or tolerability. There are no data regarding whether
testing leads to improved outcomes versus not testing in the treatment of depression; whether testing
influences medical, personal, or public health decision making; or whether any harms are associated
with testing itself or with subsequent management options.”

Chang et al. quantified the effect of functional *CYP2C19* allele variants on citalopram/escitalopram
exposure in an industry-sponsored systematic review.[94] Sixteen studies from 14 publications met the
inclusion criteria. The inclusion criteria required single- or multiple-dose citalopram or escitalopram
serum/plasma concentrations or area under the concentration-time curve (AUC) with data on *CYP2C19*
polymorphisms. Eligible studies included 847 patients from psychiatric patient trials and 140 healthy
subjects from pharmacokinetic studies. Compared to subjects with the EM/EM (*CYP2C19*1/*1) genotype, the exposure to (es)citalopram increased by 95 % (95 % CI 40-149, p < 0.0001) in the poor
metabolizer (PM)/PM (*CYP2C19*2 or *3/*2 or *3), 30 % (95 % CI 4-55, p < 0.05) in the extensive
metabolizer (EM)/PM (*CYP2C19*1/*2 or *3), and 25 % (95 % CI 1-49, p < 0.05) in the ultrarapid
metabolizer (UM)/PM (*CYP2C19*17/*2 or *3) groups. In contrast, the exposure to (es) citalopram
decreased by 36 % (95 % CI 27-46, p < 0.0001) in the UM/UM (*CYP2C19*17/*17) and by 14 % (95 %
CI 1-27, p < 0.05) in the UM/EM (*CYP2C19*17/*1). Authors reported their systematic review was the
first meta-analysis based on a systematic review of accumulated information that addresses the
relationship between *CYP2C19* genotypes and the exposure to citalopram or escitalopram.

**Nonrandomized Studies**

Although nonrandomized and retrospective studies of *CYP450* and SSRI metabolism have been
published, no prospective randomized trials of genotype-directed SSRI selection or dosing have been
reported yet.[95-100]

**Clinical Practice Guidelines**

Currently no published clinical practice guidelines recommend *CYP450* genotyping for the selection and
dosing of citalopram, escitalopram, or other SSRIs.
Conclusions

Individuals with variants in multiple p450 genes have altered metabolism of SSRI drugs. However, the impact of genetic variants on clinical response and clinical outcomes is less clear, and the evidence is not sufficient to conclude that patients with genetic variants have reduced efficacy of SSRIs. Therefore, the clinical utility of testing for SSRI dose is uncertain.

**Tamoxifen: Managing Treatment for Women at High Risk for or With Breast Cancer**[8,101]

The cytochrome P450 (CYP450) metabolic enzyme CYP2D6 has a major role in tamoxifen (TAM) metabolism. Variant DNA gene sequences resulting in proteins with reduced or absent enzyme function may be associated with lower plasma levels of active tamoxifen metabolites, which could have an impact on TAM treatment efficacy.

Potential indications for CYP2D6 pharmacogenomic testing include patients who are to be treated with TAM (alone or prior to treatment with an aromatase inhibitor) for:

- Prevention of breast cancer in high risk women or women with DCIS
- Adjuvant treatment to prevent breast cancer recurrence
- Treatment of metastatic disease

Post-menopausal patients determined to be CYP2D6 poor metabolizers could avoid TAM therapy and be treated with aromatase inhibitors alone. Pre-menopausal patients might consider ovarian ablation.

**Literature Appraisal**

**Systematic Reviews**

In 2010, the Agency for Healthcare Research and Quality (AHRQ) carried out a systematic review of the published evidence of the CYP2D6 variants and response to tamoxifen therapy in breast cancer.[102] Sixteen publications of CYP2D6 testing met the eligibility criteria and were included in the review (15 studies in the adjuvant setting and 1 study in the metastatic setting). However, the meta-analysis was not performed due to extensive heterogeneity in the definition of slow, intermediate, and extreme metabolizers across eligible studies. Instead, the results from individual studies on the strength of the association between CYP2D6 testing results and clinical outcomes were presented. The assessment concluded the following:

- There were no consistent associations between CYP2D6 polymorphism status and outcomes in tamoxifen-treated women with breast cancer across 16 studies included in the review.
- The reviewed studies were generally small in size, followed poor analytic practices, and differed both in the direction and in the formal statistical significance of their results.
- It is questionable whether pharmacogenetic testing of germline variations in CYP2D6 can predict differential response to adjuvant tamoxifen in women with non-metastatic breast cancer.
- Evidence is severely limited for tamoxifen-treated women with metastatic disease.

Based on a 2008 BlueCross BlueShield Association Technology Evaluation Center Assessment, results from clinical validity studies of CYP2D6 for use in tamoxifen management are uncertain.[101] Evidence from two higher quality trials of adjuvant TAM in relatively homogeneous patient populations suggests
that women treated with TAM who are functional poor metabolizers or intermediate metabolizers, whether by genotype or by co-medication with CYP2D6 inhibitors, have significantly reduced time to recurrence and recurrence-free survival (but not overall survival) compared to extensive metabolizers. The significance levels are marginal but might have been stronger and more convincing if poor metabolizers alone could have been compared to extensive metabolizers, but numbers of poor metabolizers were insufficient. Few variant alleles have been typed in these studies; more extensive genotyping and better categorization might also strengthen results.

The International Tamoxifen Pharmacogenomics Consortium was established to address the controversy regarding cytochrome P450 2D6 (CYP2D6) status and clinical outcomes in tamoxifen therapy. Authors from this consortium performed a meta-analysis on data from 4,973 tamoxifen-treated patients (12 globally distributed sites). [103] Using strict eligibility requirements (postmenopausal women with estrogen receptor-positive breast cancer, receiving 20 mg/day tamoxifen for 5 years, criterion 1); CYP2D6 poor metabolizer status was associated with poorer invasive disease-free survival (IDFS: hazard ratio = 1.25; 95% confidence interval = 1.06, 1.47; P = 0.009). However, CYP2D6 status was not statistically significant when tamoxifen duration, menopausal status, and annual follow-up were not specified (criterion 2, n = 2,443; P = 0.25) or when no exclusions were applied (criterion 3, n = 4,935; P = 0.38). Authors concluded, although CYP2D6 is a strong predictor of IDFS using strict inclusion criteria, because the results are not robust to inclusion criteria (these were not defined a priori), prospective studies are necessary to fully establish the value of CYP2D6 genotyping in tamoxifen therapy.

Nonrandomized Studies

Although nonrandomized and/or retrospective studies have been published, no prospective randomized clinical trials have been conducted that provide direct evidence of the clinical utility of genotype-directed tamoxifen treatment management for women at high risk for or with breast cancer. Further, nonrandomized studies have been reporting conflicting findings regarding the role of CYP2D6 mutational status in the selection and dosing of tamoxifen, with some in support [104-117] and others not. [118-124]

Clinical Practice Guidelines

Currently no published clinical practice guidelines recommend CYP450 genotyping for the selection and dosing of tamoxifen.

National Comprehensive Cancer Network

The 2015 National Comprehensive Cancer Network (NCCN) guidelines stated that, “based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy.” [21]

Conclusions

The available evidence does not clearly support a significant association between CYP2D6 genotype and tamoxifen treatment outcome; an indirect evidence chain supporting the clinical utility of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer cannot be constructed.

Tetrabenazine for Huntington disease
Tetrabenazine (Xenazine) is a monoamine depleter and reduces the amount of certain chemicals in the brain (e.g. dopamine, norepinephrine, and serotonin) to reduce chorea, or involuntary muscle movements, in Huntington disease. Its primary metabolites are metabolized mainly by \textit{CYP2D6}, and people with \textit{CYP2D6} poor metabolizer genotypes should be treated with lower doses.

\textbf{Literature Appraisal}

\textit{Nonrandomized studies}

In 2013, Mehanna et al. published results from a study that performed sequential \textit{CYP2D6} genotyping on 127 patients treated with tetrabenazine.\textsuperscript{[125]} The majority of patients (\(n = 100\)) were categorized as extensive metabolizers, 14 as intermediate metabolizers, 11 as poor metabolizers, and two as ultrarapid metabolizers. Ultrarapid metabolizer patients needed a longer titration (8 vs 3.3, 4.4, and 3 weeks, respectively; \(P < .01\)) to achieve optimal benefit and required a higher average daily dose than the other patients, but this difference did not reach statistical significance. The treatment response was less robust in the intermediate metabolizer group when compared with the extensive metabolizer patients (\(P = .013\)), but there were no statistically significant differences between the various groups with regard to adverse effects. Therefore the current recommendation to systematically genotype all patients prescribed more than 50 mg/day of tetrabenazine should be reconsidered.

\textit{U.S Food and Drug Administration (FDA) Safety Communication}

In 2015, the FDA published a warning labeling for tetrabenazine includes recommendations for genotyping for \textit{CYP2D6} for patients who are being considered for doses above 50 mg per day. The labeling states: “Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme \textit{CYP2D6} to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM). Maximum daily dose in PMs: 50 mg with a maximum single dose of 25 mg. Maximum daily dose in EMs and intermediate metabolizers (IMs): 100 mg with a maximum single dose of 37.5 mg.”\textsuperscript{[126]}

\textbf{Clinical Practice Guidelines}

Currently, there are no published clinical practice guidelines address \textit{CYP2D6} genotyping for chorea in HD.

\textbf{Conclusions}

There is limited published evidence regarding the outcomes changes associated with genotype-directed therapy for tetrabenazine in Huntington disease; however, given the FDA labeling and high variation in drug exposure based on metabolizer status, \textit{CYP2D6} to determine metabolizer status before the use of tetrabenazine when a dosage greater than 50 mg per day may be considered medically necessary.

\textbf{Tricyclic Antidepressants}

Nortriptyline and other tricyclic antidepressants (TCA) are metabolized by the \textit{CYP2D6} enzyme. Patients who are poor metabolizers (PMs) will develop serum concentrations of nortriptylline that are 3-10 fold higher than patients who are extensive metabolizers (EM).\textsuperscript{[127]}
Literature Appraisal

Nonrandomized Studies

In 2011, de Vos et al. studied 678 patients treated with TCAs and reported that EMs had increased metabolism and lower serum levels of amitriptyline and citalopram, but not clomipramine.\[128\] However, these authors reported that the differences observed were not likely to have clinically important effects.

In the study by Hodgson et al. previously discussed, CYP2D6 genotype was associated with nortriptyline levels, but not with clinical improvement in 161 patients treated with nortriptyline.\[100\]

It has been reported that patients with TCA overdose may have different risk depending on cytochrome p450 genetic status.\[128,129\] Simulations and case reports have reported that PMs may be at higher risk for toxic levels of nortriptyline, and that toxic levels are maintained for longer periods of time. There are no clinical studies that demonstrate that measuring genetic status improves outcomes for patients who have had a TCA overdose.

Clinical Practice Guidelines

Currently no published clinical practice guidelines recommend CYP450 genotyping for the selection and dosing of tricyclic antidepressants (TCA).

Conclusions

Cytochrome p450 genetic status affects the metabolism and serum levels of multiple TCAs, including nortriptyline, but the clinical impact of these differences in metabolism are not clear. There is some evidence to suggest that patients who are PMs are more prone to toxic levels in the setting of a TCA overdose. There is no evidence available to support that prospective testing of patients treated with TCAs improves outcomes.

Warfarin Dosing and Management\[7\]

Warfarin (Coumadin®) is administered for preventing and treating thromboembolic events in high-risk individuals. Dosing of warfarin is a challenging process, due to narrow therapeutic windows, variable response to dosing, and serious bleeding events.

Stable or maintenance warfarin dose varies significantly among individuals. Factors influencing stable dose include body mass index (BMI), age, interacting drugs, and indication for therapy. In addition, genetic variants of CYP450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genes together account for a substantial proportion of variability:

- Genetic variants of CYP2C9 result in enzymes with decreased activity, increased serum warfarin concentration at standard doses, and a higher risk of serious bleeding.
- VKORC1 genetic variants alter the degree of warfarin effect on its molecular target and are associated with differences in maintenance doses.

The purpose of CYP2C9 and VKORC1 genetic testing is to predict an individual’s likely maintenance warfarin dose by incorporating demographic, clinical, and genotype data. Warfarin is then initiated at that predicted dose as a way to limit over-anticoagulation and increased risk of serious bleeding events.
Regulatory Status

In 2010, the U.S. Food and Drug Administration (FDA) updated labeling for Coumadin® to include information on personalizing initial dose according to genotyping results for $CYP2C9$ and $VKORC1$. However, the information on genetic variation is not included in the black box warning and the label indicates that genetic testing is not required.

Literature Appraisal

Systematic Reviews

Five systematic reviews with meta-analyses of RCTs were published in 2014 and 2015.\textsuperscript{[130-134]} The included RCTs compared genotype-guided warfarin dosing with other dose selection strategies. The RCTs overlapped across analyses, though not all RCTs were included in all analyses. Meta-analyses used random effects models or fixed effects models when statistical heterogeneity ($I^2$) was 0%. Most studies were included in all systematic reviews.

Two systematic reviews\textsuperscript{[130,131]} included the same nine RCTs\textsuperscript{[41,135-142]} comparing genotype-guided versus clinically-guided warfarin dosing (N=2812); the RCTs were rated as high quality. Range of follow-up duration was 4 to 24 weeks (median 12 weeks). Publication bias was not detected. With one exception, pooled results from both systematic reviews were consistent. There was no statistical difference between dosing strategies in the percentage of time that the INR was in therapeutic range ($I^2=89\%$), the proportion of INRs that exceeded 4 ($I^2=0\%$), or thromboembolic events ($I^2=0\%$). However, Stergiopoulos et al. found no difference in major bleeding events (pooled relative risk [RR]=0.60 [95% CI, 0.29 to 1.22]; $I^2=0\%$), while Franchini et al. found reduced major bleeding events with genotype-guided warfarin dosing (pooled RR=0.48 [95% CI, 0.23 to 0.97]; $I^2=0\%$). This inconsistency may be attributed to the exclusion of the EU-PACT trial\textsuperscript{[136]} (N=455) from the analysis of major bleeding in Franchini et al. systematic review\textsuperscript{115}; EU-PACT reported no major bleeding events in either warfarin dosing group.

Goulding et al. reported improved clinical outcomes with genotype-guided versus other (i.e., fixed or clinically-guided) warfarin dosing.\textsuperscript{[132]} Literature was reviewed through December 2013; nine RCTs were included, seven of which overlapped with the systematic reviews previously described, and six of which were rated high or very high quality. Range of follow-up duration was 2 to 12 weeks. Pooled mean difference in the percentage of time within the therapeutic range (TTR) was 6.67 percentage points (95% CI, 1.34 to 12.00; $I^2=80\%$). However, this meta-analysis included one trial\textsuperscript{[143]} that showed benefit of genotype-guided dosing compared with fixed initial warfarin dosing (2.5 mg/day), and excluded two trials\textsuperscript{[135,139]} that showed no benefit of genotype-guided dosing compared with clinically-guided dosing. Meta-analysis also showed decreased risk of bleeding or thromboembolic events with genotype-guided dosing (pooled risk ratio=0.57 [95% CI, 0.33 to 0.99]; $I^2=60\%$).

In an analysis of eight RCTs Xu et al. reported a significantly increased TTR for genotype-guided dosing compared to fixed initial dose, but no significant difference between genotype-guided and clinically-guided dosing. The authors also reported no significant between-group differences in adverse events. The authors noted high between-group participant heterogeneity that hindered pooled estimates.

Liao et al. reported increased TTR with genotype-guided dosing compared with fixed initial warfarin dosing (three RCTs; $I^2=48\%$) but not compared with clinically-guided dosing (two RCTs; $I^2=0\%$).\textsuperscript{[133]}
These authors also found no overall difference between pooled groups in adverse events (major bleeding defined as a decrease in hemoglobin $\geq 2$ g/dL, clinically relevant non-major bleeding, thromboembolism, myocardial infarction, death from any cause, or other condition requiring emergency medical management; four RCTs; $I^2=0\%$) or mortality (three RCTs; $I^2=10\%$).

Prior systematic reviews and meta-analyses focused on analysis of associations between $CYP2C9$ and $VKORC1$ gene variants and warfarin dosing.

The 2009 Agency for Healthcare Research and Quality (AHRQ) Technology assessment of selected pharmacogenetic tests for non-cancer and cancer conditions included a systematic review of the published evidence of $CYP2C9$ and $VKORC1$ gene polymorphisms and response to warfarin therapy (29 studies of $CYP2C9$ and 19 studies of $VKORC1$ polymorphisms).[144] The review concluded the following:

- Carriers of the $CYP2C9$ gene variant alleles *2 or *3 require lower mean maintenance warfarin doses than do non-carriers.
- Few studies investigated the relationship between genetic variations in $CYP2C9$ or $VKORC1$ and warfarin dose requirements in the induction phase. $CYP2C9$ variants were associated with an increased rate of bleeding complications during the induction phase of warfarin therapy, but the studies did not report whether affected patients had normal or supratherapeutic NR ranges.
- The clinical utility of genetic testing for $CYP2C9$ in everyday clinical practice is not straightforward.
- It is unclear whether dose-prediction algorithms using genetic information improve clinical outcomes over those of standard practice. Only three RCT addressed this question, but all had flaws in design and inclusion criteria, and had inadequate power to reach statistical conclusions.
- Carriers of the three common $VKORC1$ variants (alleles T, G, and C) required lower mean maintenance doses of warfarin than did non-carriers. Data were not adequate to address any other questions.

New genetic associations such as $CYP4F2$ are under investigation and evaluating interactions among $CYP2C9$, $VKORC1$, and this new variant along with gene-environmental interactions may result in better risk predictive instruments for clinical use.

A systematic review commissioned by the American College of Medical Genetics (ACMG), evaluated $CYP2C9$ and $VKORC1$ genetic testing prior to warfarin dosing and concluded that no large study had yet shown this to be acceptable or effective.[145] Several randomized trials were noted to be underway to determine the clinical utility of testing.

Jorgensen and others investigated the influence of $CYP2C9$ and $VKORC1$ on patient response to warfarin in a 2012 systematic review and meta-analysis of 117 studies.[146] Authors concluded that genetic associations with warfarin response vary between ethnicities. In addition authors suggest that a high level of methodological rigor must be maintained and studies should report sufficient data to enable inclusion in meta-analyses and achieve unbiased estimates in different populations.

A systematic review and meta-analysis by Liang et al. suggested a more substantial contribution of $CYP4F2$ genetic variants.[147] Compared with wild type patients, carriers of $CYP4F2$ variants required warfarin doses 11% and 21% higher for heterozygous and homozygous patients, respectively.

**Randomized Controlled Trials (RCTs)**
No RCTs have been published since those included in the systematic reviews summarized above.

Nonrandomized Studies

A number of nonrandomized and retrospective studies of genotype-based vs. standard warfarin dosing have been published, including preliminary findings in children.[148-162] However, evidence from these studies does not permit conclusions due to methodological limitations such as non-random allocation of dosing management and lack of appropriate comparison groups.[148-159]

Clinical Practice Guidelines

The 2012 American College of Chest Physicians evidence-based clinical practice guidelines on “Antithrombotic Therapy and Prevention of Thrombosis,” states, “For patients initiating VKA [vitamin K antagonist] therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B).”[163]

Per the 2008 statement from the American College of Medical genetics (ACMG), “there is insufficient evidence at this time to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naive patients.”[164]

Conclusions

Genetic testing may help predict the initial warfarin dose within the first week of warfarin treatment, but the evidence does not support the conclusion that clinically relevant outcomes, such as rates of bleeding or thromboembolism, are improved. Proposed dosing algorithms require evaluation in large, prospective, randomized trials comparing genotype-guided dosing with current standard-of-care approaches to determine net health benefit.

Summary

Antipsychotics Selection and Dosing:

Evidence on genotype-directed antipsychotic selection or dosing is limited to a small number of nonrandomized studies. Clinical utility of CYP450 genotyping has not been demonstrated for this indication; it is not known how the genotyping results impact patient management, treatment plans, or health outcomes. Therefore, CYP450 genotyping for selection or dosing of antipsychotic drugs is considered investigational.

Anti-tuberculosis Medications

Evidence on an association between CYP2E1 status and the risk of liver toxicity from anti-tuberculosis medications is limited. The clinical utility of CYP450 genotyping, or whether genetic testing can reduce liver damage from anti-tuberculosis medications, compared to the usual strategy of monitoring liver enzymes and adjusting medications based on enzyme levels has not been demonstrated. Therefore, CYP450 genotyping for the management of anti-tuberculosis medications is considered investigational.

Beta Blocker Selection and Dosing:
Evidence on genotype-directed beta blocker selection and dosing is limited to a small number of nonrandomized studies that report contradictory findings. Clinical utility of CYP450 (including CYP2D6) genotyping has not been demonstrated for this indication; it is not known how the genotyping results impact patient management, treatment plans, or health outcomes. Therefore, CYP450 (including CYP2D6) genotyping for selection or dosing of beta blockers is considered investigational.

**Clopidogrel - Determining Risk of Atherothrombotic Events After an Acute Coronary Syndrome or a Percutaneous Coronary Intervention:**

Individuals with genetic variants of CYP450 have a decreased ability to metabolize clopidogrel; however it remains uncertain whether this results in a clinically meaningful change in health outcomes. Specifically, the evidence from scientific studies has not shown that genetic testing to select or dose clopidogrel leads to improved health outcomes. For stent thrombosis, it is not clear that alternate management strategies such as increasing clopidogrel dose will result in improved outcomes. Despite this lack of evidence, FDA labeling recommends cytochrome p450 genetic testing for selection and dosing of clopidogrel (Plavix®). Therefore, CYP450 genotyping may be considered medically necessary to guide selection and dose management of clopidogrel.

**Codeine Prescription for Nursing Mothers:**

The relationship between genetic variants of CYP450 (including CYP2D6) and codeine metabolism in nursing mothers has not been established. Therefore, CYP450 (including CYP2D6) for codeine selection and dosing is considered investigational.

**Efavirenz Dosing For the Treatment of HIV Infection:**

A small number of nonrandomized studies have suggested an association between CYP2B6 polymorphisms and efavirenz clearance and/or severity of side effects in patients treated with efavirenz. However, clinical utility for CYP2B6 testing has not been established; it is not known how the genotyping results impact patient management, treatment plans, or health outcomes. Therefore, CYP450 genotyping (including CYP2B6) to select or dose efavirenz is considered investigational.

**Eliglustat (Cerdelga™) for Gaucher disease type I:**

Individuals with genetic variants of CYP450 have an increased ability to metabolize eliglustat, a small-molecule oral glucosylceramide analogue that inhibits the enzyme glucosylceramide synthase was for the treatment of Gaucher disease type 1. Although the current evidence is limited to industry-sponsored nonrandomized studies on the efficacy of eliglustat, FDA labeling recommends cytochrome p450 genetic testing for selection and dosing of eliglustat. Therefore, CYP450 genotyping may be considered medically necessary to guide selection and dose management of eliglustat.

**H. pylori Infection:**

Individuals with polymorphisms in the CYP2C19 gene, a member of the CYP450 family, metabolize proton pump inhibitors (PPIs) more slowly than normal; however, based on the current evidence, it is not known whether the use of a pharmacogenomics-based treatment regimen for H. pylori improves eradication rates. Due to limited scientific evidence from RCTs, clinical utility of CYP450 (CYP2C19) genotyping has not been established; it is not known how the genotyping results impact patient
management, treatment plans, or health outcomes. Therefore, \textit{CYP450} genotyping (including \textit{CYP2C19}) to select or dose PPIs is considered investigational.

**Immunosuppressant Dosing For Organ Transplantation:**

Currently, there is limited evidence on the impact of \textit{CYP450} genotype testing (including \textit{CYP3A5}) on dosing of immunosuppressant medications. Clinical utility for \textit{CYP450} (including \textit{CYP3A5}) testing has not been established; it is not known how the genotyping results impact patient management, treatment plans, or health outcomes. Therefore, \textit{CYP450} genotyping (including \textit{CYP3A5}) to select or dose immunosuppressant drugs is considered investigational.

**Selective Norepinephrine Reuptake Inhibitors (SNRIs) Selection and Dosing:**

- \textit{Atomoxetine HCl} dosing for the treatment of attention-deficit/hyperactivity disorder (ADHD):
  Evidence on genotype-directed Atomoxetine prescribing and dose management is limited to a small number of nonrandomized studies. Clinical utility of \textit{CYP450} (including \textit{CYP2D6}) genotyping has not been demonstrated for this indication; it is not known how the genotyping results impact patient management, treatment plans, or ADHD-related health outcomes. Therefore, \textit{CYP450} (including \textit{CYP2D6}) genotyping for selection or dosing of Atomoxetine is considered investigational.
- \textit{Venlafaxine, duloxetine, and nefazodone}:
  SNRI metabolism is affected by genetic status of cytochrome p450, with the greatest potential clinical effect seen for venlafaxine. However, no studies have yet established that outcomes are improved as a result of genetic testing prior to initiating venlafaxine or other SNRIs. Therefore, \textit{CYP450} genotyping for selection or dosing of venlafaxine, duloxetine, nefazodone, or other SNRIs is considered investigational.

**Selective Serotonin Reuptake Inhibitors (SSRIs) Selection and Dosing:**

Individuals with variants in multiple \textit{CYP450} genes (eg, \textit{CYP2D6} and \textit{CYP2C19}) have altered metabolism of SSRI drugs. However, the evidence is insufficient to establish how the presence of these genetic variants affects clinical response to SSRI. Clinical utility for \textit{CYP450} (including \textit{CYP2D6} and \textit{CYP2C19}) testing has not been established; it is not known how the genotyping results impact patient management, treatment plans, or health outcomes. Therefore, \textit{CYP450} genotyping (including \textit{CYP2D6} and \textit{CYP2C19}) for selection and dosing of SSRIs is considered investigational.

**Tamoxifen - Managing Treatment for Women at High Risk For or With Breast Cancer:**

The published data on the association between \textit{CYP2D6} genotype and tamoxifen treatment outcome have yielded inconsistent results. Some of the inconsistencies in the literature may be due to differences across studies in the types of additional therapies patients were receiving, how many and which \textit{CYP2D6} alleles were tested, and coadministration of \textit{CYP2D6} inhibitors. Therefore, \textit{CYP450} genotyping (eg, \textit{CYP2D6}) for selection and dosing of tamoxifen is considered investigational.

**Tetrabenazine for Huntington disease**

There is limited published evidence regarding the outcomes changes associated with genotype-directed therapy for tetrabenazine in Huntington disease; however, given the FDA labeling and high variation in drug exposure based on metabolizer status, \textit{CYP2D6} to determine metabolizer status before the use of tetrabenazine when a dosage greater than 50mg per day may be considered medically necessary.
Tricyclic Antidepressants:

Cytochrome p450 genetic status affects the metabolism and serum levels of multiple TCAs, including nortriptyline; however, the clinical impact of these differences in metabolism are not clear. There is some evidence to suggest that patients who are poor metabolizers are more prone to toxic levels in the setting of a TCA overdose. There is no evidence available to support that prospective testing of patients treated with TCAs improves outcomes. Therefore, CYP450 genotyping to select or dose tricyclic antidepressants is considered investigational.

Warfarin Dosing and Management:

While the evidence supports a strong association between genetic variants and stable warfarin dose, and to a lesser extent, between genetic variants and International Normalized Ratio (INR) and bleeding outcomes, the evidence is not sufficient to conclude that testing for CYP2C9 and VKORC1 (and possibly CYP4F2) genetic variants improves health outcomes. Genetic testing may help predict the initial warfarin dose within the first week of warfarin treatment, but the evidence does not support the conclusion that clinically relevant outcomes, such as rates of bleeding or thromboembolism, are improved. Therefore, genotyping for variants to predict initial warfarin dose is considered investigational.

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**CROSS REFERENCES**

*Genetic and Molecular Diagnostic Testing*, Genetic Testing, Policy No. 20


**NOTE:** enter drug name in the search bar to find appropriate policy.
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