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Medical Policy Manual Genetic Testing, Policy No. 10

Cytochrome p450 and VKORC1 Genotyping for Treatment Selection and Dosing

Effective: May 1, 2021

Next Review: February 2022
Last Review: March 2021

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

CYP450 and *VKORC1* genotyping may help to tailor drug selection and dosing to individual patients based on their predicted drug metabolism. The goal of this testing it to lead to early selection and optimal dosing of the most effective drugs, while minimizing treatment failures or toxicities.

MEDICAL POLICY CRITERIA

Note: For panel testing related to behavioral health disorders, including medication selection, please refer to Genetic Testing Policy No. 53, Genetic Testing for Diagnosis and Management of Behavioral Health Conditions.

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 (CerdelgaTM); 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 *CYP2C9, CYP2C19, CYP2D6, and CYP4F2)* and *VKORC1* genotyping is considered **investigational** for medication selection and dose management, including but not limited to:

A. Panels that include testing for more than one *CYP450* gene

B. Testing for the following: anti-tuberculosis medications, atomoxetine HCl, anti-tuberculosis medications, atomoxetine HCl, beta blockers, codeine, efavirenz, H. pylori infection, immunosuppressant for organ transplantation, tamoxifen, and warfarin.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Genetic Testing for Diagnosis and Management of Behavioral Health Conditions, Medical Policy Manual, Genetic Testing, Policy No. 53
3. Genetic Testing for Epilepsy, Genetic Testing, Policy No. 80
4. Medication Policy Manual, Note: Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

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 (PMs)
  - 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 (IMs)
  - Have one active and one inactive *CYP450* enzyme gene allele
- Ultrarapid metabolizers (UMs)
  - 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.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[2] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

Following is a summary of the key literature. 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.

ANTI-TUBERCULOSIS MEDICATIONS

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

Systematic Reviews

Wang (2016) reported a meta-analysis of 26 studies with a total of 7,423 participants, evaluating the association of *CYP2E1* variants and susceptibility to antituberculosis drug-induced hepatotoxicity. The overall odds ratios of relevant studies demonstrated that the *CYP2E1 RsaI/PstI C1/C1* genotype was associated with an elevated risk of liver toxicity (odds ratio [OR] 1.32, 95% confidence interval [CI] 1.03 to 1.69, p=0.027), but for the *DraI* variant there was no increase in risk (OR 1.05, 95% CI 0.80 to 1.37, p=0.748).

In a meta-analysis, Sheng (2014) investigated the potential association between cytochrome P450 2E1 (*CYP2E1*) polymorphisms and the risk of anti-tuberculosis drug-induced hepatotoxicity (ATDH).[3] Compared with the wild genotype (*C1/C1*), the OR of ATDH was 1.41 (95% CI 1.1 to 1.82, p=0.007) for the *PstI/RsaI* polymorphism, and 0.78 (95% CI 0.51 to 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 (2013).[4] Compared with wild type genotype, patients with any variant genotype had an increased risk of liver toxicity (OR 1.36, 95% CI 1.09 to 1.69). Patients who were slow metabolizers had the highest risk of toxicity (OR 1.88, 95% CI 1.14 to 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.

Randomized Controlled Trials

No randomized controlled trials (RCTs) evaluating the clinical utility of *CYP450* testing for use in prescribing anti-tuberculosis medications were identified.

Nonrandomized Studies

Evidence of the relationship between *CYP450* genotype and ATDH is limited to small observational studies.[5-7]

Section Summary

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

BETA BLOCKER SELECTION AND DOSING

Systematic Reviews

A systematic review by Mottet (2016) examined the influence of pharmacogenetics on heart failure treatment.[8] The authors noted that while studies indicate that *CYP2D6* variants affect the pharmacokinetics of metoprolol, there is limited evidence on the topic and the clinical impact of the relationship has not been established.

Randomized Controlled Trials

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. Some have reported that *CYP2D6* variants are associated with altered responses to these medications,[9, 10] with a few studies indicating that lipophilic beta selective adrenergic receptor antagonists, such as metoprolol used in treating hypertension, may exhibit impaired elimination in patients with *CYP2D6* polymorphisms.[11-15] In addition, increased risk of bradycardia was observed in patients found to be PMs (*CYP2D6 *4/*4*), although the clinical significance of this observation remains to be defined.[11, 16, 17]

In contrast, it has also been reported that no difference in response to metoprolol or carvedilol was observed according to genotype.[18-20]

Section Summary

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 the enzyme coded by *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.

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 (see below). Meta-analyses have also compared genotype-guided treatment to standard treatment in patients with acute coronary syndrome or those undergoing PCI or stent implantation, with mixed findings.[21-25] However, in the absence of a significant effect of *CYP2C19* variants on clopidogrel efficacy, it is not clear what mechanisms would lead to outcome differences.

Wang (2016) reported results of a meta-analysis of 12 studies involving 8,284 patients to evaluate the association between *CYP3A5* variants and the risk of adverse events in patients undergoing clopidogrel therapy.[26] The *CYP3A5* variant was classified as wild-type, heterozygote, and homozygous variant. There was no statistically significant difference in the odds of major adverse cardiovascular events in the three groups classified by *CYP3A5* variant (wild-type plus heterozygote vs. homozygous variant: OR 1.032, 95% CI 0.583 to 1.824, p=0.915, wild-type vs. heterozygote plus homozygous variant: OR 1.415, 95% CI 0.393 to 5.094, p=0.595). There was no significant relation between *CYP3A5* variants and bleeding (homozygous vs. wild-type plus heterozygote: OR 0.798, 95% CI 0.370 to 1.721, p=0.565) or clopidogrel resistance (wild-type plus heterozygote vs. homozygous variant: OR 1.009, 95% CI 0.685 to 1.488, p=0.963; wild-type vs. heterozygote plus homozygous variant: OR 0.618, 95% CI 0.368 to 1.039, p=0.069).

Osnabrugge (2015) reported a systematic review of 11 meta-analyses which summarized studies evaluating the associations between *CYP2C19* genetic status and outcomes in clopidogrel-treated patients.[27] 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.

Mao (2013) 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.[28] 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 noncarriers (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 myocardial infarction (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).

Bauer (2011) 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.[29] 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 noncarriers, 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.”

Holmes (2011) systematically reviewed studies linking *CYP2C19* testing to treatment with clopidogrel.[30] 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 (2012) noted that the results of the Holmes (2011) analysis may have been compromised by the fact that patients who did not undergo percutaneous coronary intervention (PCI) were included.[31] 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.[32] 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.

Xi (2017) published a systematic review and meta-analysis on *CYP2C19* genotype and adverse outcomes with clopidogrel treatment following stent implantations in Asian populations.[33] Twenty studies with a total of 15,056 patients were included. MACE, a composite outcome of myocardial infarction and cardiovascular death, was the primary outcome assessed. Patients that had at least one loss-of-function allele had an increased risk of MACE compared with noncarriers (OR 1.99, 95% CI 1.64 to 2.42, p<0.001), and a reduced risk of bleeding (OR 0.66, 95% CI 0.46 to 0.96, p<0.001). Subgroup analysis indicated that risk of MACE was significantly elevated for patients with a loss-of-function allele among those who had a high loading dose of clopidogrel (600 mg).

Randomized Controlled Trials

Pereira (2020) published results of the TAILOR-PCI randomized trial comparing genotype-guided antiplatelet therapy to standard clopidogrel therapy in 5,302 patients undergoing PCI for acute coronary syndromes or stable coronary artery disease.[34] This was a multicenter trial carried out in the US, Canada, Mexico, and South Korea. Patients in the genotype-guided group who had a loss-of-function *CYP2C19* allele received ticagrelor, while noncarriers and those in the control group received clopidogrel. The primary outcome of the trial was a composite of cardiovascular death, stroke, myocardial infarction, stent thrombosis, and severe recurrent ischemia at one year. Major and minor bleeding were also assessed. No significant differences were seen for the primary outcome, which occurred in 113/2,641 (4.4%) of the genotype-guided group and 135/2,635 (5.3%) of the control group (HR 0.84, 95% CI 0.65 to 1.07, p=0.16), or any of the 11 prespecified secondary outcomes.

A randomized trial by Claassens (2019) assigned 2,488 patients undergoing PCI to receive either genotype-guided (n=1,242) or standard selection (n=1,246) of oral platelet inhibitors.[35] For the genotype-guided group, patients carrying *CYP2C19*2* or *CYP2C19*3* loss-of-function alleles were treated with ticagrelor or prasugrel, while non-carriers were treated with clopidogrel. The two primary outcomes of this trial were an adverse event composite of death from any cause, myocardial infarction, stent thrombosis, stroke or major bleeding and a bleeding outcome composed of major or minor bleeding at 12 months according to Platelet Inhibition and Patient Outcomes (PLATO) criteria. A non-inferiority analysis indicated that the genotype-guided treatment selection was not inferior to standard treatment selection for the adverse events and was associated with a lower incidence of bleeding (hazard ratio [HR] 0.78, 95% CI 0.61 to 0.98, p=0.04). A prespecified subanalysis of this study found that the *CYP2C19*17* variant was not associated with the thrombotic or bleeding outcomes.[36]

Roberts (2012) reported on the use of a point-of-care *CYP2C19*C* genetic test for treatment selection (standard treatment [prasugrel] versus clopidogrel).[37] In this controlled trial, patients undergoing 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. Noncarriers and all patients in the control group were given 75 mg of clopidogrel per day. The primary endpoint was high on-treatment platelet reactivity. 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.

Han (2017) evaluated the impact of *CYP2C19* genotype in a randomized trial designed to compare the effects of triflusal and clopidogrel in patients with a first-time, non-cardiogenic stroke.[38] The study included 784 patients that were randomized 1:1 to either triflusal or clopidogrel, and the primary endpoint was recurrent stroke (ischemic or hemorrhagic). The median follow-up was 2.7 years, and 597 (76%) of patients completed the trial. There were no significant differences found for individuals with a poor-metabolizer *CYP2C19* genotype (**2/*2*, **2/*3*, or **3/*3*, n=484) by treatment group. Additionally, there were no significant differences in outcomes between genotype groups. However, the authors noted that the required sample size for the study (n=1,080) was not reached.

So (2016) tested a pharmacogenomic strategy to guide anti-platelet therapy in patients with ST-elevation myocardial infarction.[39] There were 102 patients enrolled in the study and they received point-of-care genetic testing for *CYP2C19**2, *ABCB1 TT* and *CYP2C19*17*. Those with either the *CYP2C19*2* or the *ABCB1 TT* allele were randomly assigned to either prasugrel 10 mg daily or an augmented clopidogrel strategy (150 mg daily for six days, then 75 mg daily). The primary endpoint of this trial was high on-treatment platelet reactivity (HPR). There were 59 patients that were carriers of at least one of the two variants. Among these, those randomized to prasugrel treatment had reduced rates of HPR compared to the clopidogrel treatment group (P2Y12 reaction unit thresholds of >234: 0 vs. 24.1%, p=0.0046; and PRU>208:3.3 vs. 34.5%, p=0.0025, respectively). While the results of this study indicate that prasugrel treatment may be superior to clopidogrel treatment in carriers, the effects of the pharmacogenomic strategy itself were not tested in this trial, as there was no group randomized to a non-pharmacogenomic strategy.

Wang (2016) evaluated the association between *CYP2C19* loss-of-function alleles and the efficacy of clopidogrel in patients with minor stroke or transient ischemic attack.[40] In this trial, 2,933 Chinese patients were randomized to treatment with either clopidogrel plus aspirin or aspirin alone. *CYP2C19* genotype and clinical outcomes including new stroke, other vascular events, and bleeding were assessed. There were 1,726 carriers identified with a loss-of-function allele. After 90 days of follow-up, the clopidogrel plus aspirin treatment was more effective in preventing new stroke than aspirin alone only in noncarriers (non-carrier HR 0.51, 95% CI 0.35 to 0.75; carrier HR 0.93, 95% CI 0.69 to 1.26, p=0.02 for interaction). Similar results were seen for other vascular outcomes. Bleeding was more common in the clopidogrel plus aspirin treatment group than the aspirin only group, but there was no difference by carrier status (2.3% for carriers and 2.5% for noncarriers in the clopidogrel-aspirin group vs. 1.4% for carriers and 1.7% for noncarriers in the aspirin only group, p=0.78 for interaction). These results indicate that for carriers of a *CYP2C19* loss-of-function allele, treatment with aspirin alone may result in better outcomes than combined clopidogrel and aspirin treatment.

Zhang (2016) compared the efficacy and safety of ticagrelor and high-dose clopidogrel in 181 patients with acute coronary syndrome that were intermediate or PMs of clopidogrel in an open-label randomized trial.[41] The primary study outcome was a composite outcome of death, stroke, recurrent myocardial infarction, and stent thrombosis. This outcome occurred in 4.4% of the patients in the ticagrelor group compared with 20.0% if the high-dose clopidogrel group

(p<0.001). There was no significant difference in bleeding between the treatment groups. The authors concluded that ticagrelor may be a safer and more efficacious treatment than high-dose clopidogrel in patients that are intermediate or PMs.

Similarly, Doll (2016) evaluated the impact of *CYP2C19* variants in acute coronary syndrome patients randomized to treatment with either prasugrel or clopidogrel.[42] This study was a substudy of the double-blind TRILOGY ACS trial, which included 9,326 patients from 52 countries who had unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI). Of these, 5,736 patients participated in the genetics cohort, and a subset of 2,236 of these additionally participated in a platelet function substudy. Patients were classified as either extensive metabolizers (EM) or reduced metabolizers (RM) based on their *CYP2C19* genotype. The primary study endpoint was a composite of cardiovascular death, recurrent myocardial infarction, or stroke, and there was not difference between metabolizer status groups or treatment groups for this outcome. In multivariate analysis, EM patients had a reduced risk of myocardial infarction compared with RM patients (HR: 0.80), but other individual outcomes were similar. Among patients treated with clopidogrel, RM patients had significantly higher platelet reactivity than EM patients. There was no such difference among those treated with prasugrel.

Pare (2010) retrospectively genotyped 5,059 patients from two large randomized trials (the Clopidogrel in Unstable Angina to Prevent Recurrent Events or “CURE” trial and the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events or “Active” trial) that showed clopidogrel reducing the rate of cardiovascular events when compared with placebo in patients with acute coronary syndromes and atrial fibrillation.[43] Genotyping was performed for **2*, **3*, and **17* of the *CYP2C19* allele. These investigators observed that the efficacy and safety of clopidogrel 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. Although the reason for these divergent findings remains unclear, it was noted that in the populations studied, use of stents was substantially less than in previous reports (19% of patients with acute coronary syndromes and only 14.5% in patients with atrial fibrillation).

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.[44-53] However, others have not found such an association.[54-56] 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.[43] Even when data were restricted to evaluation of patients homozygous for loss of function, no increased risk of cardiovascular events was observed. One study of patients with symptomatic intracranial atherosclerotic disease found lower odds of thrombotic events or death in individuals with a loss-of-function allele.[57]

Recent studies have suggested that changes in platelet reactivity in carriers may be dose-dependent,[58, 59] and that in PCI patients, heterozygous carriers might require up to triple dosing of clopidogrel to reach a desired target platelet reactivity level.[60, 61] In homozygous carriers, it has been reported that even with higher clopidogrel doses, platelet reactivity cannot be reduced to the level achieved with clopidogrel treatment in noncarriers. In these

patients, other drugs such as prasugrel or ticagrelor may be used as treatment alternatives. However, not all studies have found a difference in platelet response to clopidogrel based on *CYP2C16* genotype.[62]

Cavallari (2018) reported outcomes among 1,815 PCI patients at multiple centers who had antiplatelet therapy guided by *CYP2C19* testing.[63] For individuals with a loss-of-function allele, alternative antiplatelet therapies (prasugrel, ticagrelor) were recommended instead of clopidogrel. Patients were followed for major cardiovascular events (myocardial infarction, stroke, or death) for 12 months following PCI. Among the 572 (31.2%) of patients with a loss-of-function allele, the risk for cardiovascular events was significantly higher in those patients prescribed clopidogrel instead of alternative therapy (adjusted HR 2.26, 95% confidence interval 1.18 to 4.32, p=0.013). There was no difference in cardiovascular events between patients with a loss-of-function allele prescribed alternative therapy and patients without a loss-of-function allele.

Desai (2013) 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.[64] Among the 146 subjects (30%) with at least one *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 PMs 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.[61, 65]

Section Summary

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.

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 UMs of codeine due to a cytochrome *CYP2D6* polymorphism, the 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."[66]

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.”[44]

Section Summary

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 (CNS) effects. While most resolve in the first few weeks of treatment, about 6% of patients discontinue efavirenz due to adverse effects.[67] 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.

Systematic Reviews

No systematic reviews of genotype-directed efavirenz dosing for the treatment of HIV infection have been identified.

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* PMs have markedly reduced side effects while maintaining viral immunosuppression at substantially lower doses.[68, 69] Simulations of such dose adjustments support this position.[70] 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.

Gross (2017) assessed the role of *CYP2B6* genotypes in an observational cohort study of efavirenz-based regimens in Botswana.[71] The primary endpoint of the study was a composite of death, loss to care, or HIV RNA above 25 copies/ml at six months. Among the 801 participants, the slow-metabolism alleles were associated with reduced efavirenz clearance, but not with the study outcomes or CNS toxicity.

Cabrera (2009) reported on an evaluation in 32 patients of the relationship between *CYP2B6* polymorphisms and efavirenz clearance.[72] Although they reported that *CYP2B6* polymorphisms accounted 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.

Gallien (2017) assessed the role of *CYP2B6* polymorphisms and efavirenz-induced CNS symptoms in a substudy of the ANRS ALIZE trial that included 191 patients.[73] The authors reported a association between the *CYP2B6 516T* allele and higher plasma efavirenz levels, and the occurrence of a first central nervous system event.

Two studies have been published that demonstrated an association between markers and early efavirenz discontinuation: one evaluating 373 patients for polymorphisms in *CYP2B6* and constitutive androstane receptor (CAR)[1], and one evaluating genotyping for 23 markers in 15 genes[65]. Both articles recommended further study to determine the clinical utility of these associations.

Lee (2014) evaluated the effect of *CYP2B6* G516T polymorphisms on the plasma efavirenz concentrations in HIV-infected patients, with or without concomitant rifampicin use.[74] The study included 171 HIV-infected patients including 18 with tuberculosis, 113 (66.1%) with *CYP2B6 G516G*, 55 (32.2%) with *G/T*, and 3 (1.8%) with *T/T* genotype. Patients with *G/T* or *T/T* genotype had a significantly higher plasma efavirenz concentration than those with *G/G* genotype (2.50 vs. 3.47 mg/L for *G/T* genotype and 8.78 mg/L for *T/T* genotype; $p<0.001$).

Bienvenu (2014) evaluated the effect of single nucleotide polymorphisms (SNPs) in five 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).[75] 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.

A small cohort study by Bolton Moore (2017) compared genotype-directed efavirenz dosing to a pharmacokinetic model of efavirenz exposure based on FDA-approved doses in young children aged 3 to 36 months.[76] This analysis predicted that genotype-directed dosing would avoid subtherapeutic levels in nearly one-third of those with a *516GG/GT* genotype and excessive levels in more than half of those with *516T/T* genotypes.

A study by Mollan (2017) evaluated the relationship between *CYP2B6* and *CYP2A6* genotypes and risk of suicide in four efavirenz clinical trials, and found that genotypes associated with higher plasma efavirenz levels were also associated with suicide risk.[77] The association was strongest among white participants.

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 (2013) found that polymorphisms in *CYP2B6*, but not in *CYP3A4* and *CYP3A5*, were associated with SJS risk.[78] Additionally, in a prospective cohort study including 66 women receiving nevirapine, Oluka (2015). reported that *CYP2B6* genotype was associated with serum nevirapine concentration and CD4 counts.[79] Finally, Lu (2014) reported that *CYP3A5* polymorphisms are associated with serum concentrations of maraviroc, a CCR5 receptor antagonist used for HIV treatment, in healthy control subjects.[80]

Section Summary

Genetic variants in *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 *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.[81] 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 *CYP2D6* and, therefore, *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 *CYP2D6* genotype, will not be eligible for eliglustat treatment.

There are no published studies that demonstrate how genotyping results for *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 *CYP2D6*. The FDA labeling requires that patients be selected on the basis of *CYP2D6* metabolizer status as determined by genotype, with recommendations based on genotype about dosage and concomitant use of *CYP2D6* and *CYP3A* inhibitors.[82]

Section Summary

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 *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 PMs.

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 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.[83]

Systematic Reviews

Tang (2013) 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.[84] 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 to 0.881), between HomEMs and PMs (OR 0.507, 95% CI 0.379 to 0.679), or between HetEMs and PMs (OR 0.688, 95% CI 0.515 to 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 to 0.553) or lansoprazole (OR 0.692, 95% CI 0.485 to 0.988), and also in HomEMs vs. PMs for omeprazole (OR 0.232, 95% CI 0.105 to 0.515) or lansoprazole (OR 0.441, 95% CI 0.252 to 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

A randomized, controlled trial comparing a pharmacogenomics-based treatment regimen with a standard regimen was evaluated.[85] 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."

A similar trial by Zhou (2016) compared tailored therapy, based on *CYP2C19* genotype and clarithromycin sensitivity, to triple therapy plus bismuth and concomitant therapy.[86] In this study, 1,050 *H. pylori* patients at three tertiary hospitals in China were randomized to ten days of one of the three treatment regimens. While the authors reported a significantly higher eradication rate in the tailored treatment group in the setting of high antibiotic resistance rates, this study has many of the same limitations noted for the Japanese study described above.

A much smaller trial by Arévalo Galvis (2019) found no significant difference between triple therapy with standard omeprazole compared with personalized therapy based on *CYP2C19* genotype.[87] This trial included 133 patients in Columbia.

Additional RCTs evaluating *H. pylori* eradication rates for different treatment regimens reported that the *CYP2C19* genotype appears to play a role in eradication rates,[88-90] though not all trials have found this to be the case.[91] However, these trials were not designed to compare a pharmacogenomics-based treatment regimen with a standard regimen.

Nonrandomized Studies

Several nonrandomized studies have evaluated the impact of *CYP2C19* variants on PPI metabolism, *H. pylori* eradication, and ulcer healing.[92-95] These studies have had mixed results. 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.[88, 96-107]

Section Summary

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.

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.[108] *CYP3A5*1* carriers have been reported to have a significant delay in reaching target tacrolimus concentrations compared to noncarriers. Although the overall rate of acute rejection episodes was not higher in *CYP3A5*1* carriers, their rejection episodes did occur earlier.[109]

Population-based pharmacokinetic models for clearance of tacrolimus in kidney transplant recipients have been developed for both adult and children.[110, 111] 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.

Systematic Reviews

A meta-analysis by Hendijani (2018) focused on the effect of *CYP3A5*1* expression on tacrolimus dose in pediatric transplant patients.[112] Data from 11 studies (n=596) were included. The results of the analysis indicated that *CYP3A5*1* expressers required a tacrolimus dose that was 0.06 mg/kg/day higher to achieve the same blood level as non-expressers.

Rojas (2015) 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.[113] It is important to note that this review only included observational studies thereby precluding firm conclusions. A similar meta-analysis by Khan (2020) of kidney transplant recipients reported that *CYP3A5* genotype was significantly associated with the trough concentration-dose ratio, but not with allograft rejection in European patients.[114]

In a meta-analysis, Rojas (2013) investigated the effect of the *CYP3A5 6986A>G* polymorphism in liver donors and transplant recipients on tacrolimus pharmacokinetics.[115] 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 (2014) 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.[116] 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 (2010) conducted an RCT to compare the proportion of tacrolimus-treated renal transplant patients within a targeted C0 range for two tacrolimus dosing strategies, *CYP3A5* genotype-informed dosing or standard dosing.[117] 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 six 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.

An RCT by Min (2018) evaluating genotype-guided tacrolimus dosing after pediatric solid organ transplantation showed similar results to the Thervet (2010) trial regarding reduced time to targeted therapeutic tacrolimus concentrations with the guided approach, but was similarly not powered to assess differences in health outcomes.[118]

Nonrandomized Studies

Passey (2011) 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.[119] The study's final model included *CYP3A5* genotype, along with other clinical factors, but was not validated in an independent population. A similar, but smaller study (n=59) was published by Woillard (2017), which used *CYP3A4* and *CYP3A5* alleles for model development.[120]

Boughton (2013) evaluated the model developed by Passey (2011)[119] in a single-center cohort of renal transplant recipients.[121] The study found a weak correlation (*R*=0.431) between clearance based on dose-normalized tacrolimus trough concentrations and the algorithm-predicted clearance.

Tapirdamaz (2014) 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).[122] 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 (2014) found no significant effect of *CYP3A5* genotype on the rate of acute cellular rejection between postoperative days 14 and 23.[123] 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.

Kato (2016) reported long-term outcomes for 67 donor/recipient couples and their relation to tacrolimus pharmacokinetics and *CYP3A5* genotype.[124] Donor/recipient couples from 2002 to 2009 with tacrolimus administration were included in the study. Recipients who had a **1* allele and/or who had a donor with a **1* allele required significantly higher doses of the drug than those couples without the allele. Additionally, five-year survival rates for recipients with two **1* alleles were significantly worse than for those with a **1*3* or a **3*3* genotype (28.6% vs. 78.8% and 84.3%, respectively).

Section Summary

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.

TAMOXIFEN: MANAGING TREATMENT FOR WOMEN AT HIGH RISK FOR OR WITH BREAST CANCER[125, 126]

The 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 highirisk women or women with ductal carcinoma in situ (DCIS)
- Adjuvant treatment to prevent breast cancer recurrence
- Treatment of metastatic disease

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

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.[127] There were 16 publications of *CYP2D6* testing met the eligibility criteria and were included in the review (15 studies in the adjuvant setting and one 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, 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.

A 2008 BlueCross BlueShield Association Technology Evaluation Center Assessment, found that evidence from clinical validity studies of *CYP2D6* for use in tamoxifen management was uncertain.[126] Results from two higher quality trials of adjuvant TAM in relatively homogeneous patient populations suggest that women treated with TAM who are functional PMs or IMs, 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 PMs alone could have been compared to extensive metabolizers, but numbers of PMs 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 *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).[128] Using strict eligibility requirements (postmenopausal women with estrogen receptor-positive breast cancer, receiving 20 mg/day tamoxifen for five years, criterion 1); *CYP2D6* poor metabolizer status was associated with poorer invasive disease-free survival (IDFS HR 1.25, 95% CI 1.06 to 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.

Drögemöller (2019) conducted a systematic review of the association between *CYP2D6* genetic variation and survival outcomes after tamoxifen treatment.[129] Included studies showed conflicting conclusions. In multivariate analyses, there was no significant relationship between survival outcomes and the confounders of sample size (p=0.83), ethnicity (p=0.33), or source

of DNA (p=0.14). Comprehensive genotyping panels were more likely to report a significant association with *CYP2D6*-survival outcome: 11 of 13 studies that used comprehensive genotyping found a significant association between *CYP2D6* and survival outcomes. Limitations of the studies identified by the review authors included differences in survival outcome definitions, differences in metabolizer group classifications, low consent rates, and not controlling for CYP2D6-inhibitor use. Data in most of these studies were derived from a convenience sample, which was further limited by relatively small numbers of patients and lack of comprehensive genotype data, patient data (e.g., concomitant medications), and detailed clinical outcomes data.

Lu (2017) published a meta-analysis of studies evaluating the role of *CYP2D6 *10* genotype on clinical outcomes for Asian women treated with tamoxifen for breast cancer.[130] The *CYP2D6 *10 T/T* genotype has been linked to low enzyme activity. Fifteen studies with a total of 1,794 patients were included. Pooled analysis of the effect of the *CYP2D6 *10* genotype identified significant associations with disease-free survival in several comparison models (*TT* vs. *CC*: HR 1.79, 95% CI 1.14 to 2.80, p=0.011; *CT* vs. *CC*: HR 2.02, 95% CI 1.04 to 3.19, p=0.037; *TT* vs. *CT*: HR 2.03, 95% CI 1.41 to 2.93, p<0.001; *TT* vs. *CT/CC*: HR 2.19, 95% CI 1.07 to 4.50, p=0.033).

Randomized Controlled Trials

One trial of genotype-directed dosing that assessed outcomes of breast cancer recurrence was identified. The RCT, published by Tamura (2020) was a phase II, proof-of-concept study performed at multiple centers in Japan.[131] A total of 184 patients were included in this study, of which 136 had at least one *CYP2D6* variant-type allele. Only one patient classified as a poor metabolizer with two null alleles was included in this trial. The results of this trial did not find a significant difference in outcomes between increased tamoxifen dosing and standard dosing in patients with *CYP2D6* genotypic variants Nonrandomized Studies

Nonrandomized studies have reported conflicting findings regarding the role of *CYP2D6* variant status in the selection and dosing of tamoxifen, with some in support[132-145] and others not.[146-154]

Among the most influential studies of the association between *CYP2D6* genotype and tamoxifen effectiveness are three nonconcurrent, prospective studies nested within large RCTs that compared tamoxifen with anastrozole, letrozole, or combination tamoxifen and anastrozole in postmenopausal women with hormone receptor-positive early-stage breast cancer. In the Arimidex, Tamoxifen, Alone or in Combination trial,[147] and Breast International Group 1-98 trial,[146] a subset of patients who received tamoxifen and were genotyped for *CYP2D6* variants (n=588 and n=1,243, respectively) did not show any statistically significant associations between phenotype (patients classified as poor, intermediate, or extensive metabolizer) and breast cancer recurrence. In the Austrian Breast and Colorectal Cancer Study Group trial, a case-control study was done using a subset of patients where cases were defined as those with disease recurrence, contralateral breast cancer, second non-breast cancer, or died and controls were identified from the same treatment arm of similar age, surgery/radiation, and stage.[155] Results showed that patients with two poor-metabolizer alleles had a higher likelihood of recurrence than women with two extensive-metabolizer alleles. Concerns about the substantial departure from Hardy-Weinberg equilibrium for the *CYP2D6* allele, *4 and analyses not meeting the Simon-Paik-Hayes criteria for nonconcurrent prospective studies

have been raised to explain the lack of effect in the Arimidex, Tamoxifen, Alone or in Combination trial and Breast International Group 1-98 trials.[156]

Section Summary

The evidence for *CYP2D6* genotype-guided tamoxifen treatment includes one RCT, several meta-analyses and systematic reviews, multiple nonrandomized studies. Published data on the association between *CYP2D6* genotype and tamoxifen treatment outcomes have yielded inconsistent results. Data in most of these studies were derived from a convenience sample, which was further limited by relatively small numbers of patients and lack of comprehensive genotype data, patient data, and detailed clinical outcomes data. Three influential nonconcurrent prospective studies nested within large RCTs that included postmenopausal women with hormone receptor-positive early-stage breast cancer also reported contradictory results, with two larger studies failing to show statistically significant associations between phenotype (patients classified as poor, intermediate, or extensive metabolizer) and recurrence of breast cancer. The RCT examining genotype-directed dosing found no difference in progression free survival between standard dose and increased dose; however, this trial was limited by its proof-of-concept design. No trials of genotype-directed drug choice that compared health outcomes for patients managed with and without the test were identified. It is not known whether *CYP2D6* genotype-guided tamoxifen treatment results in the selection of a treatment strategy that would reduce the rate of breast cancer recurrence, improve disease-free survival or OS, or reduce adverse events. 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 *CYP2D6*, and people with *CYP2D6* poor metabolizer genotypes should be treated with lower doses.

Systematic Reviews

No systematic reviews of *CYP2D6* genotyping for tetrabenazine management were identified.

Randomized Controlled Trials

There were no RCTs reported for this indication.

Nonrandomized studies

Mehanna (2013) published results from a study that performed sequential *CYP2D6* genotyping on 127 patients treated with tetrabenazine.[157] The majority of patients (n=100) were categorized as extensive metabolizers, 14 as IMs, 11 as PMs, and two as ultrarapid metabolizers (UMs). UMs 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.

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

In 2015, the FDA published a warning labeling for tetrabenazine includes recommendations for genotyping for *CYP2D6* for patients who are being considered for doses above 50 mg per day. The labeling states: “Patients should be genotyped for CY2D6 prior to treatment with daily doses of tetrabenazine over 50 mg.”[158]

Section Summary

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, *CYP2D6* to determine metabolizer status before the use of tetrabenazine when a dosage greater than 50 mg per day may be considered medically necessary.

WARFARIN DOSING AND MANAGEMENT[159]

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 to limit over-anticoagulation and increased risk of serious bleeding events.

Regulatory Status

In 2010, the 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.

Systematic Reviews

The Washington Health Care Authority completed a technology assessment of pharmacogenetic testing for anticoagulants in 2018, which included 13 RCTs.[160] In the meta-analysis of mortality, thromboembolic events, and major bleeding, no differences between groups were seen in mortality or thromboembolism but there was a reduction in major bleeding seen in the pharmacogenetic testing group. There were no statistically significant differences in the percentage of time in therapeutic range or overanticoagulation. The authors noted that the evidence for the thromboembolic events was rated as moderate quality, while the evidence for the other outcomes was low quality.

A meta-analysis by Yang (2019) included 15 RCTs (total n=4,852) evaluating genotype-guided warfarin dosing.[161] The primary outcome of the analysis was the percentage time in therapeutic range (PTTR). Within a one-month follow-up period, there was no significant difference in PTTR between genotype-guided and control (fixed initial dosage) groups, based on data from eight trials. Three trials reported on PTTR at three months, which was significantly higher for the genotype-guided patients compared to controls (weighted mean difference 5.62%, 95% CI 2.33% to 8.90%, p=0.001). Genotype-guided patients also had a shorter time to first therapeutic international normalized ratio (INR), shorter time to stable therapeutic dose, and decreased risk of warfarin-related major bleeding events. No differences were seen for thromboembolism risk, bleeding events, and all-cause mortality. The authors completed a risk of bias assessment of included studies. All trials claimed to be randomized, however, the random sequence generation was only explicitly described in nine studies. Only seven studies discussed allocation concealment, and blinding was not implemented in most of the included RCTs.

A network meta-analysis by Sridharan (2020) compared three different genotyping strategies for warfarin dosing: *CYP2C9* alone, *CYP2C9* with *VKORC1*, and *CYP2C9* with both *VKORC1* and *CYP4F2*.[162] The analysis included data from 28 RCTs, and the primary outcomes were the time to first therapeutic INR, time to stable INR or warfarin dose, PTTR, and the proportion of patients with supra-therapeutic INR. The results of the meta-analysis indicated that the *CYP2C9*-alone strategy and the *CYP2C9* with *VKORC1* strategy were associated with a shorter time to first therapeutic INR and stable INR/warfarin dose, while only the *CYP2C9* with *VKORC1* strategy was associated with a greater PTTR.

Tse (2018) published a meta-analysis of 18 trials of genotype-guided versus standard warfarin dosing.[163] The analysis included 2,626 patients in the genotype-guided group and 2,604 patients in the control group, and the mean follow-up duration was 64 days. Genotype-guided dosing was associated with a shorter time to therapeutic international normalized ratio (INR) (mean difference 2.6 days, p<0.0001, I^2 0%) and stable INR (mean difference 5.9 days, p<0.01, I^2 94%), but no difference was seen in thromboembolism or mortality. Similar results were seen in a meta-analysis by Kheiri (2018) that included 20 RCTs.[164]

Five systematic reviews with meta-analyses of RCTs were published in 2014 and 2015.[165-170] 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[165, 166] included the same nine RCTs[66, 171-178] comparing genotype-guided versus clinically-guided warfarin dosing (n=2,812); 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 (2014) 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 (2014) 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[172] (n=455) from the analysis of major bleeding in Franchini (2014)

systematic review; EU-PACT reported no major bleeding events in either warfarin dosing group.

Goulding (2014) reported improved clinical outcomes with genotype-guided versus other (i.e., fixed or clinically-guided) warfarin dosing.[167] 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[179] that showed benefit of genotype-guided dosing compared with fixed initial warfarin dosing (2.5 mg/day), and excluded two trials[171, 175] 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 (2014) 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 (2015) 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%).[168] These authors also found no overall difference between pooled groups in adverse events (major bleeding [defined as a decrease in hemoglobin ≥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%).

A systematic review by Zhang (2017) evaluated *CYP2C9* polymorphisms and warfarin maintenance dosage in pediatric patients.[180] The review included eight studies with a total of 507 patients. Of these, five studies investigated the role of the *CYP2C9 *1/*2* genotype, and meta-analysis indicated that this genotype was associated with warfarin maintenance dose that was 15% lower than that for patients with *CYP2C9 *1/*1.* In five studies that evaluated the *CYP2C9 *1/*3,* this genotype was associated with 41% lower maintenance dose compared with **1/*1*. However, this study did not evaluate the use of genotyping in pediatric warfarin dose selection.

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).[181] The review concluded the following:

- Carriers of the *CYP2C9* gene variant alleles **2* or **3* require lower mean maintenance warfarin doses than do noncarriers.
- 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 INR 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 noncarriers. 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.[182]

Jorgensen (2012) investigated the influence of *CYP2C9* and *VKORC1* on patient response to warfarin in a systematic review and meta-analysis of 117 studies.[183] 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 that 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 (2012) suggested a more substantial contribution of *CYP4F2* genetic variants.[184] 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

A total of 24 RCTs comparing genotype-guided with clinical dosing of warfarin were identified. Twenty-two of these RCTs were included in at least one systematic review. We identified two additional RCTs not included in any of the systematic reviews.[185, 186] Neither found a difference between groups in the percent of time in therapeutic range. One of the two trials reported major bleeding outcomes and found no significant difference between genotype-guided and traditional dosing.[185]

Nonrandomized Studies

A number of nonrandomized and retrospective studies of genotype-based vs. standard warfarin dosing have been published,[187] including preliminary findings in children.[188-202] 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.[188-199]

Section Summary

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.

PRACTICE GUIDELINE SUMMARY

ANTI-TUBERCULOSIS MEDICATIONS

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

BETA BLOCKER SELECTION AND DOSING

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

CLOPIDOGREL: DETERMINING RISK OF ATHEROTHROMBOTIC EVENTS AFTER AN ACUTE CORONARY SYNDROME OR A PERCUTANEOUS CORONARY INTERVENTION

American College of Cardiology (ACC) foundation and the American Heart Association (AHA)

A consensus statement by the American College of Cardiology (ACC) foundation and the American Heart Association (AHA) on genetic testing for selection and dosing of clopidogrel was published in 2010.[203] 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.

SELECTION OR DOSING OF CODEINE

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

DOSE AND SELECTION OF HIGHLY ACTIVE ANTIRETROVIRAL AGENTS

There are currently no published clinical practice guidelines recommend *CYP450* genotyping for the dosing of efavirenz.

ELIGLUSTAT (CERDELGA™) FOR GAUCHER DISEASE TYPE I.

Currently no published clinical practice guidelines recommend *CYP2D6* genotyping for the dosing of eliglustat.

H. PYLORI INFECTION

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

IMMUNOSUPPRESSANT DOSING FOR ORGAN TRANSPLANTATION

Currently no published clinical practice guidelines recommend *CYP450* genotyping for the dosing of immunosuppressant medications**.**

TAMOXIFEN: MANAGING TREATMENT FOR WOMEN AT HIGH RISK FOR OR WITH BREAST CANCER

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

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer (v.4.2018) state that, “CYP2D6 genotype testing is not recommended in women who are considering tamoxifen.”[27]

American Society of Clinical Oncology

The 2016 guideline on the use of biomarkers to guide adjuvant systemic therapy decisions for women with early-stage invasive breast cancer states that, “The clinician should not use cytochrome P450 2D6 (*CYP2D6*) polymorphisms to guide adjuvant endocrine therapy selection.”

TETRABENAZINE FOR HUNTINGTON DISEASE

Currently, there are no published clinical practice guidelines address *CYP2D6* genotyping for chorea in HD.

WARFARIN DOSING AND MANAGEMENT

American College of Chest Physicians

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).”[204]

American College of Medical Genetics

Per the 2008 statement from the American College of Medical genetics, “there is insufficient evidence at this time to recommend for or against routine *CYP2C9* and *VKORC1* testing in warfarin-naive patients.”[205]

SUMMARY

ANTI-TUBERCULOSIS MEDICATIONS:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients taking anti-tuberculosis medications. There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* genotyping for the management of anti-tuberculosis medications is considered investigational.

BETA BLOCKER SELECTION AND DOSING:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients taking beta blockers. There are no clinical guidelines based on research that recommend genetic testing for this purpose. 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:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients taking anti-tuberculosis medications. Despite this, 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:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients taking codeine, including nursing mothers. There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* (including *CYP2D6*) for codeine selection and dosing is considered investigational.

EFAVIRENZ DOSING FOR THE TREATMENT OF HIV INFECTION:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients taking efavirenz to treat HIV infection. There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* genotyping (including CYP2B6) to select or dose efavirenz is considered investigational.

ELIGLUSTAT (CERDELGA™) FOR GAUCHER DISEASE TYPE I:

There is very little research on *CYP450* genetic testing for people with Gaucher disease considering eliglustat. However, 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:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for people with *H. pylori* infections taking proton pump inhibitors (PPIs). There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* genotyping (including *CYP2C19*) to select or dose PPIs is considered investigational.

IMMUNOSUPPRESSANT DOSING FOR ORGAN TRANSPLANTATION:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for organ transplantation patients taking immunosuppressant medications. There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* genotyping (including *CYP3A5*) to select or dose immunosuppressant drugs is considered investigational.

TAMOXIFEN - MANAGING TREATMENT FOR WOMEN AT HIGH RISK FOR OR WITH BREAST CANCER:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients with breast cancer or at high risk for breast cancer that are considering tamoxifen treatment. Additionally, there are clinical guidelines based on research that specifically recommend against genetic testing for this purpose. Therefore, *CYP450* genotyping (e.g., *CYP2D6*) for selection and dosing of tamoxifen is considered investigational.

TETRABENAZINE FOR HUNTINGTON DISEASE

There is very little research showing how genetic testing can help with tetrabenazine dosing decisions. However, because of the FDA labeling for the medication and evidence that genetics can greatly affect the metabolism of the medication, *CYP2D6* testing to determine metabolizer status may be considered medically necessary before the use of tetrabenazine, when a dosage greater than 50mg per day may be considered.

WARFARIN DOSING AND MANAGEMENT:

There is research that shows that *CYP2C9* and *VKORC1* genes are related to warfarin dosing, but there is not enough research to show that genetic testing for these genes improves health outcomes for people taking this medication. Therefore, genotyping for variants to predict initial warfarin dose is considered investigational.

OTHER INDICATIONS

CYP2C19 testing may be useful for selecting anti-platelet treatments, and CYP2D6 testing can aid in medication selection for patients with Gaucher or Huntington disease. While testing for various CYP450 genes has been proposed to help with selection of other medications, there is not enough research to show that this testing is helpful for guiding medication selection and improving health outcomes for patients. In addition, there are no

clinical guidelines based on research that recommend such testing. Therefore, CYP450 genetic testing that does not meet the policy criteria is considered investigational.

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CODES

Codes	Number	Description
CPT	0015U	Drug metabolism (adverse drug reactions), DNA, 22 drug metabolism and transporter genes, real-time PCR, blood or buccal swab, genotype and metabolizer status for therapeutic decision support
	0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, *CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1* and rs12777823)
	0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, *CYP2C9, CYP4F2, VKORC1*, rs12777823)
	0031U	*CYP1A2* (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7)
	0070U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, common and select rare variants (ie, *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
	0071U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
	0072U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)
	0073U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
	0074U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)
	0075U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)

Codes	Number	Description
	0076U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/ multiplication) (List separately in addition to code for primary procedure)
	81225	*CYP2C19* (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
	81226	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
	81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
	81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)
	81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)
	81355	*VKORC1* (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
	81401	Molecular pathology procedure, Level 2
	81402	Molecular pathology procedure, Level 3
	81404	Molecular pathology procedure, Level 5
	81405	Molecular pathology procedure, Level 6
HCPCS	G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

Date of Origin: *March 2011*