Cytochrome p450 and VKORC1 Genotyping for Treatment Selection and Dosing

Effective: May 1, 2024

Next Review: February 2025
Last Review: March 2024

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 (Cerdelga™); or

   B.   Huntington disease being considered for treatment with tetrabenazine (Xenazine ®) in a dosage greater than 50mg per day.

III. *CYP2C9* genotyping to determine drug metabolizer status may be considered **medically necessary** for patients with relapsing forms of multiple sclerosis (i.e., clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease) being considered for treatment with siponimod (Mayzent®).

IV. Except as defined in Criteria I, II, or III 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, 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 of testing
6. Medical records related to this genetic test:
   o History and physical exam including any relevant diagnoses related to the genetic testing
   o Date of blood draw
   o Conventional testing and outcomes
   o 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.

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.).

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.[21-27] 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.

Cargnin (2023) published a systematic review and meta-analysis that evaluated the clinical utility of *CYP2C19* genotyping in stroke and transient ischemic attack patients of non-East Asian ancestry.[28] The review investigated the association of *CYP2C19* loss-of-function status with efficacy and safety of clopidogrel-based antiplatelet therapy. Clopidogrel-treated carriers of *CYP2C19* loss-of-function alleles were found at increased risk of stroke compared to non-carriers (risk ratio [RR]: 1.68, 95%CI: 1.04 to 2.71, p= 0.03). However, no significant association was observed with the risk of composite vascular events (RR: 1.15, 95%CI: 0.58 to 2.28, p=0.69) or bleeding (RR: 0.84, 95%CI: 0.38 to 1.86, p=0.67). Similarly, European ancestry patients carrying *CYP2C19* loss-of-funcion alleles displayed a higher risk of stroke (RR: 2.69 (1.11 to 6.51, p=0.03), but not of composite vascular events or bleeding.

Malik (2022) completed a SR with meta-analysis to evaluate the effectiveness of genotype testing-guided P2Y12 inhibitor prescription therapy to patients after PCI for ACS compared to non-genotype guided conventional treatment. The analysis included seven studies (9617 patients). Genotype-guided strategy arm included prasugrel or ticagrelor prescription to patients with loss of function (LOF) of CYP219 alleles (most commonly alleles being *2 and *3) and clopidogrel prescription to those without the LOF allele. The conventional arm included patients treated with clopidogrel without genotype testing. The genotype arm showed decreased major adverse cardiovascular events, improved cardiovascular (CV) mortality,

reduced incidence of myocardial infarction (MI) and decreased incidence of stent thrombosis. Stroke incidence was similar in the two arms.[27]

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.[29] 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.[30] 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.[31] 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.[32] 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.[33] 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.[34] 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.[35] A total of 4,819 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.[36] 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.[37] 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.[38] 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.[39]

Roberts (2012) reported on the use of a point-of-care *CYP2C19*C* genetic test for treatment selection (standard treatment [prasugrel] versus clopidogrel).[40] 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.[41] 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.[42] 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.[43] 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.[44] 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.[45] 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.[46] 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.[47-56] However, others have not found such an association.[57-61] 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.[46] 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.[62]

Recent studies have suggested that changes in platelet reactivity in carriers may be dose-dependent,[63, 64] and that in PCI patients, heterozygous carriers might require up to triple dosing of clopidogrel to reach a desired target platelet reactivity level.[65, 66] 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.[67]

Cavallari (2018) reported outcomes among 1,815 PCI patients at multiple centers who had antiplatelet therapy guided by CYP2C19 testing.[68] 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.[69] 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.[66, 70]

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."[71]

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."[47]

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.[72] 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.[73, 74] Simulations of such dose adjustments support this position.[75] 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.[76] 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.[77] 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.[78] The authors reported an 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[70]. 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.[79] 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).[80] 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.[81] 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.[82] 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.[83] 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.[84] 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.[85]

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^{TM}) 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.[86] 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.[87]

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.[88]

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.[89] Authors identified 16 RCT datasets derived from 3,680 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.

Similar results were seen in a meta-analysis by Morino (2021), which included 25 RCTs of PPI-amoxicillin-clarithromycin regimen among different *CYP2C19* genotypes.[90] In an intention-to-treat analysis, eradication rates were highest among poor metabolizers (86.8% [644/742], 95% CI 83.9 to 88.9%), followed by intermediate (81.2% [1,498/1,844], 95% CI 79.3 to 83.0%) and extensive metabolizers (77.7% [1,137/1,464], 95% CI 75.3 to 79.6%), but these were not significantly different (p=0.696). This analysis also pooled various drug regimens, limiting generalizability.

Randomized Controlled Trials

Choi (2022) published the results of a double-blind, controlled, multicenter study to evaluate whether tegoprazan (50 mg)-based triple therapy (TPZ) was noninferior to lansoprazole (30 mg)- based triple therapy (LPZ) for treating H. pylori. The primary endpoint was the H. pylori eradication rate. Subgroup analyses were performed according to the cytochrome P450 (CYP) 2C19 genotype, the minimum inhibitory concentration (MIC) of amoxicillin and clarithromycin, and underlying gastric diseases. Subgroup analyses according to MICs or CYP2C19 did not show differences in eradication rate.[91]

A randomized, controlled trial comparing a pharmacogenomics-based treatment regimen with a standard regimen was evaluated.[92] 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.[93] 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.[94] 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,[95-97] though not all trials have found this to be the case.[98] 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.[99-102] 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.[95, 103-114]

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.[115] *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.[116]

Population-based pharmacokinetic models for clearance of tacrolimus in kidney transplant recipients have been developed for both adult and children.[117, 118] 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

Yang (2021) published a systematic review and meta-analysis of RCTs comparing genotype-guided and conventional tacrolimus dosing in kidney transplant patients.[119] Five RCTs with a total of 684 patients were included, and all trials were judged to be of high quality using GRADE methodology. The proportion of patients with a tacrolimus exposure within the therapeutic range at steady state, which was the primary outcome, was higher among the genotype-guided group (relative risk [RR] 1.40, 95% CI 1.14 to 1.72, p=0.001). However, there were no significant differences between groups in the health outcomes assessed, including incidences of acute graft rejection, delayed graft function, adverse events, or graft survival censored for death, suggesting that there "was no utility in pharmacogenetics for tacrolimus based on the [*CYP3A5*]."

A meta-analysis by Hendijani (2018) focused on the effect of *CYP3A5*1* expression on tacrolimus dose in pediatric transplant patients.[120] 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.[121] 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.[122]

In a meta-analysis, Rojas (2013) investigated the effect of the *CYP3A5 6986A>G* polymorphism in liver donors and transplant recipients on tacrolimus pharmacokinetics.[123] 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.[124] 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.[125] 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.[126]

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.[127] 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.[128]

Boughton (2013) evaluated the model developed by Passey (2011)[127] in a single-center cohort of renal transplant recipients.[129] 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).[130] 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.[131] 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.[132] 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[133]

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 high risk 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.[134] 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.[135] 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).[136] 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.[137] 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.[138] 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.[139] 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[140-153] and others not.[154-163]

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,[155] and Breast International Group 1-98 trial,[154] 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.[164] 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.[165]

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.[166] 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."[167]

Section Summary

There is limited published evidence regarding the changes in outcomes 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.

SIPONIMOD FOR MULTIPLE SCLEROSIS

The FDA has approved siponimod for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The recommended maintenance dosage is 2 mg. The recommended maintenance dosage in patients with a *CYP2C9*1/*3* or *2/*3* genotype is 1 mg. Siponimod is contraindicated in patients with a *CYP2C9*3/*3* genotype.[168]

WARFARIN DOSING AND MANAGEMENT[169]

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

Wang (2022) completed a SR to analyze the impact of CYP2C19 polymorphisms on warfarin maintenance dose. Nine studies were included in the analysis (1393 patients). Three CYP2C19 SNPs were identified: rs4244285, rs4986893 and rs3814637. Warfarin maintenance dose was significantly reduced by 10% in individuals with the rs4986893 A allele compared with the GG carriers and was 34%, 16% and 18% lower in patients with rs3814637 TT and CT genotypes and T allele, respectively, than that in CC carriers. No significant dose difference was observed among the rs4244285 genotypes. The authors conclude that CYP2C19 rs4986893 and rs3814637 are associated with significantly reduced warfarin dose requirements. These results were largely driven by the Zhu (2020) RCT.[170]

The Washington Health Care Authority completed a technology assessment of pharmacogenetic testing for anticoagulants in 2018, which included 13 RCTs.[171] 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 over-anticoagulation. 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.[172] 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 and Sivaramakrishnan (2020) compared three different genotyping strategies for warfarin dosing: *CYP2C9* alone, *CYP2C9* with *VKORC1*, and *CYP2C9* with both *VKORC1* and *CYP4F2*.[173] 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.[174] 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.[175]

Five systematic reviews with meta-analyses of RCTs were published in 2014 and 2015.[176-181] 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[176, 177] included the same nine RCTs[71, 182-189] 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 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[183] (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.[178] 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[190] that showed benefit of genotype-guided dosing compared with fixed initial warfarin dosing (2.5 mg/day), and excluded two trials[182, 186] 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%).[179] 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.[191] 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).[192] 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.[193]

Jorgensen (2012) investigated the influence of *CYP2C9* and *VKORC1* on patient response to warfarin in a systematic review and meta-analysis of 117 studies.[194] 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.[195] 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 28 RCTs comparing genotype-guided with clinical dosing of warfarin were identified. Twenty-seven of these RCTs were included in at least one systematic review. We identified one additional RCTs not included in any of the systematic reviews. Zhu (2020) found that INR time in therapeutic range was improved with genotype-guided dosing based on *CYP2C9* and *VKORC1* compared with clinically-guided dosing in elderly Chinese patients with nonvalvular atrial fibrillation.[196] Additionally, bleeding events did not differ between groups, but ischemic stroke occurred less frequently with genotype-guided dosing.

Nonrandomized Studies

A number of nonrandomized and retrospective studies of genotype-based vs. standard warfarin dosing have been published,[197] including preliminary findings in children.[198-212] 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.[198-209]

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

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.[213] 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

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.

<u>National Comprehensive Cancer Network</u>

The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer (v.1.2024) state that, "CYP2D6 genotype testing is not recommended in women who are considering tamoxifen."[214]

<u>American Society of Clinical Oncology</u>

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 CYP2D6 polymorphisms to guide adjuvant endocrine therapy selection. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.[215]."

TETRABENAZINE FOR HUNTINGTON DISEASE

Currently no published clinical practice guidelines recommend *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)."[216]

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."[217]

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.

SIPONIMOD FOR MULTIPLE SCEROSIS

There is limited research showing how genetic testing can help with siponimod dosing decisions. However, because of the FDA labeling for the medication and evidence that genetics can greatly affect the metabolism of the medication, *CYP2C9* testing to determine metabolizer status may be considered medically necessary before the use of siponimod for patients with relapsing forms of multiple sclerosis.

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.

REFERENCES

1. Wyen C, Hendra H, Siccardi M, et al. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. *The Journal of antimicrobial chemotherapy.* 2011;66(9):2092-8. PMID: 21715435
2. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. *Human mutation.* 2016;37(6):564-9. PMID: 26931183

3. Sheng YJ, Wu G, He HY, et al. The association between CYP2E1 polymorphisms and hepatotoxicity due to anti-tuberculosis drugs: A meta-analysis. *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases.* 2014;24C:34-40. PMID: 24607341

4. Deng R, Yang T, Wang Y, et al. CYP2E1 RsaI/PstI polymorphism and risk of anti-tuberculosis drug-induced liver injury: a meta-analysis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* 2012;16(12):1574-81. PMID: 23131254

5. Heinrich MM, Zembrzuski VM, Ota MM, et al. Factors associated with anti-TB drug-induced hepatotoxicity and genetic polymorphisms in indigenous and non-indigenous populations in Brazil. *Tuberculosis (Edinburgh, Scotland).* 2016;101:15-24. PMID: 27865386

6. Perwitasari DA, Irham LM, Darmawan E, et al. CYP2E1 polymorphism, acetylator profiles and drug-induced liver injury incidence of Indonesian tuberculosis patients. *The Indian journal of tuberculosis.* 2016;63(3):139-43. PMID: 27865233

7. Ben Fredj N, Gam R, Kerkni E, et al. Risk factors of isoniazid-induced hepatotoxicity in Tunisian tuberculosis patients. *The pharmacogenomics journal.* 2016. PMID: 27089936

8. Mottet F, Vardeny O, de Denus S. Pharmacogenomics of heart failure: a systematic review. *Pharmacogenomics.* 2016;17(16):1817-58. PMID: 27813451

9. Zhang F, Duan X, Zhang M, et al. Influence of CYP2D6 and beta2-adrenergic receptor gene polymorphisms on the hemodynamic response to propranolol in Chinese Han patients with cirrhosis. *Journal of gastroenterology and hepatology.* 2016;31(4):829-34. PMID: 26489037

10. Cai J, Dai DP, Geng PW, et al. Effects of 22 Novel CYP2D6 Variants Found in the Chinese Population on the Bufuralol and Dextromethorphan Metabolisms In Vitro. *Basic & clinical pharmacology & toxicology.* 2016;118(3):190-9. PMID: 26310775

11. Bijl MJ, Visser LE, van Schaik RH, et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. *Clin Pharmacol Ther.* 2009;85(1):45-50. PMID: 18784654

12. Yuan H, Huang Z, Yang G, et al. Effects of polymorphism of the beta(1) adrenoreceptor and CYP2D6 on the therapeutic effects of metoprolol. *J Int Med Res.* 2008;36(6):1354-62. PMID: 19094446

13. Wojtczak A, Wojtczak M, Skretkowicz J. The relationship between plasma concentration of metoprolol and CYP2D6 genotype in patients with ischemic heart disease. *Pharmacological reports : PR.* 2014;66(3):511-4. PMID: 24905532

14. Batty JA, Hall AS, White HL, et al. An investigation of CYP2D6 genotype and response to metoprolol CR/XL during dose titration in patients with heart failure: a MERIT-HF substudy. *Clin Pharmacol Ther.* 2014;95(3):321-30. PMID: 24193112

15. Hefner G, Unterecker S, Shams ME, et al. Melperone but not bisoprolol or metoprolol is a clinically relevant inhibitor of CYP2D6: evidence from a therapeutic drug monitoring survey. *J Neural Transm (Vienna).* 2015;122:1609-17. PMID: 25940834

16. Hamadeh IS, Langaee TY, Dwivedi R, et al. Impact of CYP2D6 polymorphisms on clinical efficacy and tolerability of metoprolol tartrate. *Clin Pharmacol Ther.* 2014;96:175-81. PMID: 24637943

17. Mugosa S, Djordjevic N, Djukanovic N, et al. Factors affecting the development of adverse drug reactions to beta-blockers in hospitalized cardiac patient population. *Patient preference and adherence.* 2016;10:1461-9. PMID: 27536078

18.   Baudhuin LM, Miller WL, Train L, et al. Relation of ADRB1, CYP2D6, and UGT1A1 polymorphisms with dose of, and response to, carvedilol or metoprolol therapy in patients with chronic heart failure. *Am J Cardiol.* 2010;106(3):402-8. PMID: 20643254

19.   Wu D, Li G, Deng M, et al. Associations between ADRB1 and CYP2D6 gene polymorphisms and the response to beta-blocker therapy in hypertension. *J Int Med Res.* 2015;43:424-34. PMID: 25823457

20.   Zeng W, Chu T, Hu M, et al. OS 31-02 ANTIHYPERTENSIVE RESPONSE TO BISOPROLOL WAS NOT RELATED TO POLYMORPHISMS IN ADRB1 Or CYP2D6 IN CHINESE HYPERTENSIVE PATIENTS. *Journal of hypertension.* 2016;34 Suppl 1 - ISH 2016 Abstract Book:e388. PMID: 27754210

21.   Kheiri B, Osman M, Abdalla A, et al. CYP2C19 pharmacogenetics versus standard of care dosing for selecting antiplatelet therapy in patients with coronary artery disease: A meta-analysis of randomized clinical trials. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2018. PMID: 30403317

22.   Kheiri B, Abdalla A, Osman M, et al. Personalized antiplatelet therapy in patients with coronary artery disease undergoing percutaneous coronary intervention: A network meta-analysis of randomized clinical trials. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2019. PMID: 30628754

23.   Zheng L, Yang C, Xiang L, et al. Genotype-guided antiplatelet therapy compared with conventional therapy for patients with acute coronary syndromes: a systematic review and meta-analysis. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals.* 2019;24(6):517-23. PMID: 31215825

24.   Wang X, Wang S, Yang J, et al. Genotype-guided antiplatelet therapy compared with standard therapy for patients with acute coronary syndromes or undergoing percutaneous coronary intervention: A systematic review and meta-analysis. *Thrombosis research.* 2020;193:130-38. PMID: 32559569

25.   Lyu SQ, Yang YM, Zhu J, et al. The efficacy and safety of CYP2C19 genotype-guided antiplatelet therapy compared with conventional antiplatelet therapy in patients with acute coronary syndrome or undergoing percutaneous coronary intervention: A meta-analysis of randomized controlled trials. *Platelets.* 2020;31(8):971-80. PMID: 32546030

26.   Malik AH, Gupta R, Chakraborty S, et al. Effect of genotype guided oral P2Y12 inhibitor selection after percutaneous coronary intervention: A systematic review and meta-analysis of randomized clinical trials. *Cardiovasc Revasc Med.* 2022. PMID: 35033458

27.   Malik AH, Gupta R, Chakraborty S, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Cardiovasc Revasc Med.* 2022;41:115-21. PMID: 35033458

28.   Cargnin S, Ferrari F, Terrazzino S. Impact of CYP2C19 Genotype on Efficacy and Safety of Clopidogrel-based Antiplatelet Therapy in Stroke or Transient Ischemic Attack Patients: An Updated Systematic Review and Meta-analysis of Non-East Asian Studies. *Cardiovasc Drugs Ther.* 2023. PMID: 38038819

29.   Wang YQ, Wang CH, Zhang JH. Association between CYP3A5 polymorphisms and the risk of adverse events in patients undergoing clopidogrel therapy: Meta-analysis. *Thrombosis research.* 2016;147:1-6. PMID: 27649539

30.   Osnabrugge RL, Head SJ, Zijlstra F, et al. A systematic review and critical assessment of 11 discordant meta-analyses on reduced-function CYP2C19 genotype and risk of

adverse clinical outcomes in clopidogrel users. *Genet Med.* 2015;17:3-11. PMID: 24946154

31. Mao L, Jian C, Changzhi L, et al. Cytochrome CYP2C19 polymorphism and risk of adverse clinical events in clopidogrel-treated patients: a meta-analysis based on 23,035 subjects. *Archives of cardiovascular diseases.* 2013;106(10):517-27. PMID: 24080325

32. Bauer T, Bouman HJ, van Werkum JW, et al. Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. *BMJ.* 2011;343:d4588. PMID: 21816733

33. Holmes MV, Perel P, Shah T, et al. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA : the journal of the American Medical Association.* 2011;306(24):2704-14. PMID: 22203539

34. Beitelshees AL. Personalised antiplatelet treatment: a RAPIDly moving target. *Lancet.* 2012;379(9827):1680-2. PMID: 22464341

35. Bhatt DL, Pare G, Eikelboom JW, et al. The relationship between CYP2C19 polymorphisms and ischaemic and bleeding outcomes in stable outpatients: the CHARISMA genetics study. *European heart journal.* 2012;33(17):2143-50. PMID: 22450429

36. Xi Z, Fang F, Wang J, et al. CYP2C19 genotype and adverse cardiovascular outcomes after stent implantation in clopidogrel-treated Asian populations: A systematic review and meta-analysis. *Platelets.* 2017:1-12. PMID: 29257922

37. Pereira NL, Farkouh ME, So D, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. *JAMA : the journal of the American Medical Association.* 2020;324(8):761-71. PMID: 32840598

38. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A Genotype-Guided Strategy for Oral P2Y12 Inhibitors in Primary PCI. *N Engl J Med.* 2019;381(17):1621-31. PMID: 31479209

39. Claassens DMF, Bergmeijer TO, Vos GJA, et al. Clopidogrel Versus Ticagrelor or Prasugrel After Primary Percutaneous Coronary Intervention According to CYP2C19 Genotype: A POPular Genetics Subanalysis. *Circulation Cardiovascular interventions.* 2021:CIRCINTERVENTIONS120009434. PMID: 33722066

40. Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet.* 2012;379(9827):1705-11. PMID: 22464343

41. Han SW, Kim YJ, Ahn SH, et al. Effects of Triflusal and Clopidogrel on the Secondary Prevention of Stroke Based on Cytochrome P450 2C19 Genotyping. *Journal of stroke.* 2017;19(3):356-64. PMID: 29037010

42. So DY, Wells GA, McPherson R, et al. A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with ST-elevation myocardial infarction: the RAPID STEMI study. *The pharmacogenomics journal.* 2016;16(1):71-8. PMID: 25850030

43. Wang Y, Zhao X, Lin J, et al. Association Between CYP2C19 Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack. *JAMA : the journal of the American Medical Association.* 2016;316(1):70-8. PMID: 27348249

44. Zhang Y, Zhao Y, Pang M, et al. High-dose clopidogrel versus ticagrelor for treatment of acute coronary syndromes after percutaneous coronary intervention in CYP2C19

intermediate or poor metabolizers: a prospective, randomized, open-label, single-centre trial. *Acta cardiologica.* 2016;71(3):309-16. PMID: 27594126

45.   Doll JA, Neely ML, Roe MT, et al. Impact of CYP2C19 Metabolizer Status on Patients With ACS Treated With Prasugrel Versus Clopidogrel. *Journal of the American College of Cardiology.* 2016;67(8):936-47. PMID: 26916483

46.   Pare G, Mehta SR, Yusuf S, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *N Engl J Med.* 2010;363(18):1704-14. PMID: 20979470

47.   Frere C, Cuisset T, Morange PE, et al. Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. *Am J Cardiol.* 2008;101(8):1088-93. PMID: 18394438

48.   Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med.* 2009;360(4):363-75. PMID: 19106083

49.   Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med.* 2009;360(4):354-62. PMID: 19106084

50.   Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet.* 2009;373(9660):309-17. PMID: 19108880

51.   Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA : the journal of the American Medical Association.* 2009;302(8):849-57. PMID: 19706858

52.   Sibbing D, Stegherr J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. *European heart journal.* 2009;30:916-22. PMID: 19193675

53.   Kirac D, Erdem A, Avcilar T, et al. Effects of genetic factors to stent thrombosis due to clopidogrel resistance after coronary stent placement. *Cell Mol Biol (Noisy-le-grand).* 2016;62(1):51-5. PMID: 26828987

54.   Zhao Z, Li X, Sun S, et al. Impact of genetic polymorphisms related to clopidogrel or acetylsalicylic acid pharmacology on clinical outcome in Chinese patients with symptomatic extracranial or intracranial stenosis. *Eur J Clin Pharmacol.* 2016;72(10):1195-204. PMID: 27450232

55.   Gonzalez A, Moniche F, Cayuela A, et al. Effect of CYP2C19 Polymorphisms on the Platelet Response to Clopidogrel and Influence on the Effect of High Versus Standard Dose Clopidogrel in Carotid Artery Stenting. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery.* 2016;51(2):175-86. PMID: 26526111

56.   Komosa A, Siller-Matula JM, Lesiak M, et al. Association between high on-treatment platelet reactivity and occurrence of cerebral ischemic events in patients undergoing percutaneous coronary intervention. *Thrombosis research.* 2016;138:49-54. PMID: 26826508

57.   Choi IJ, Koh YS, Park MW, et al. CYP2C19 loss-of-function alleles are not associated with clinical outcome of clopidogrel therapy in patients treated with newer-generation drug-eluting stents. *Medicine.* 2016;95(26):e4049. PMID: 27368038

58.   Watanabe Y, Kozuma K, Ishikawa S, et al. Hyper-Response to Clopidogrel in Japanese Patients Undergoing Transcatheter Aortic Valve Implantation. *International heart journal.* 2016;57(2):190-7. PMID: 26973266

59.   Meschia JF, Walton RL, Farrugia LP, et al. Efficacy of Clopidogrel for Prevention of Stroke Based on CYP2C19 Allele Status in the POINT Trial. *Stroke.* 2020;51(7):2058-65. PMID: 32568642

60. Ahmed S, Gul S, Siraj S, et al. Antiplatelet response to clopidogrel is associated with a haplotype in CYP2C19 gene in Pakistani patients. *Sci Rep.* 2022;12(1):6171. PMID: 35418564

61. Madan M, Abbott JD, Lennon R, et al. Sex-Specific Differences in Clinical Outcomes After Percutaneous Coronary Intervention: Insights from the TAILOR-PCI Trial. *J Am Heart Assoc.* 2022;11(12):e024709. PMID: 35699175

62. Hoh BL, Gong Y, McDonough CW, et al. CYP2C19 and CES1 polymorphisms and efficacy of clopidogrel and aspirin dual antiplatelet therapy in patients with symptomatic intracranial atherosclerotic disease. *Journal of neurosurgery.* 2016;124(6):1746-51. PMID: 26587656

63. Ou W, He Y, Li A, et al. Genotype Frequencies of CYP2C19, P2Y12 and GPIIIa Polymorphisms in Coronary Heart Disease Patients of Han Ethnicity, and Their Impact on Clopidogrel Responsiveness. *International heart journal.* 2016;57(5):586-92. PMID: 27488401

64. Guo YM, Zhao ZC, Zhang L, et al. CYP2C19 polymorphisms in acute coronary syndrome patients undergoing clopidogrel therapy in Zhengzhou population. *Genetics and molecular research : GMR.* 2016;15(2). PMID: 27323099

65. Mega JL, Hochholzer W, Frelinger AL, 3rd, et al. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. *JAMA : the journal of the American Medical Association.* 2011;306(20):2221-8. PMID: 22088980

66. Gurbel PA, Tantry US. Do platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents?: platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents. *Circulation.* 2012;125(10):1276-87; discussion 87. PMID: 22412089

67. Wang SH, Li X, Hou FL, et al. Comparison of the antiplatelet effect of clopidogrel benzene sulfonate and clopidogrel hydrogen sulfate in stable coronary heart disease. *Genetics and molecular research : GMR.* 2016;15(2). PMID: 27173230

68. Cavallari LH, Lee CR, Beitelshees AL, et al. Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. *JACC Cardiovascular interventions.* 2018;11(2):181-91. PMID: 29102571

69. Desai NR, Canestaro WJ, Kyrychenko P, et al. Impact of CYP2C19 genetic testing on provider prescribing patterns for antiplatelet therapy after acute coronary syndromes and percutaneous coronary intervention. *Circulation Cardiovascular quality and outcomes.* 2013;6(6):694-9. PMID: 24192573

70. Lubomirov R, Colombo S, di Iulio J, et al. Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: an observational cohort study. *The Journal of infectious diseases.* 2011;203(2):246-57. PMID: 21288825

71. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med.* 2013;369(24):2283-93. PMID: 24251361

72. King J, Aberg JA. Clinical impact of patient population differences and genomic variation in efavirenz therapy. *AIDS.* 2008;22(14):1709-17. PMID: 18753940

73. Torno MS, Witt MD, Saitoh A, et al. Successful use of reduced-dose efavirenz in a patient with human immunodeficiency virus infection: case report and review of the literature. *Pharmacotherapy.* 2008;28(6):782-7. PMID: 18503405

74. Gatanaga H, Hayashida T, Tsuchiya K, et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. *Clin Infect Dis.* 2007;45(9):1230-7. PMID: 17918089

75. Nyakutira C, Roshammar D, Chigutsa E, et al. High prevalence of the CYP2B6 516G-->T(*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. *Eur J Clin Pharmacol.* 2008;64(4):357-65. PMID: 18057928

76. Gross R, Bellamy SL, Ratshaa B, et al. CYP2B6 genotypes and early efavirenz-based HIV treatment outcomes in Botswana. *AIDS.* 2017;31(15):2107-13. PMID: 28692529

77. Cabrera SE, Santos D, Valverde MP, et al. Influence of the cytochrome P450 2B6 genotype on population pharmacokinetics of efavirenz in human immunodeficiency virus patients. *Antimicrob Agents Chemother.* 2009;53:2791-8. PMID: 19433561

78. Gallien S, Journot V, Loriot MA, et al. Cytochrome 2B6 polymorphism and efavirenz-induced central nervous system symptoms : a substudy of the ANRS ALIZE trial. *HIV medicine.* 2017. PMID: 28145050

79. Lee KY, Lin SW, Sun HY, et al. Therapeutic drug monitoring and pharmacogenetic study of HIV-infected ethnic Chinese receiving efavirenz-containing antiretroviral therapy with or without rifampicin-based anti-tuberculous therapy. *PLoS One.* 2014;9:e88497. PMID: 24551111

80. Bienvenu E, Swart M, Dandara C, et al. The role of genetic polymorphisms in cytochrome P450 and effects of tuberculosis co-treatment on the predictive value of CYP2B6 SNPs and on efavirenz plasma levels in adult HIV patients. *Antiviral research.* 2014;102:44-53. PMID: 24316028

81. Bolton Moore C, Capparelli EV, Samson P, et al. CYP2B6 genotype-directed dosing is required for optimal efavirenz exposure in children 3-36 months with HIV infection. *AIDS.* 2017;31(8):1129-36. PMID: 28323755

82. Mollan KR, Tierney C, Hellwege JN, et al. Race/Ethnicity and the Pharmacogenetics of Reported Suicidality With Efavirenz Among Clinical Trials Participants. *The Journal of infectious diseases.* 2017;216(5):554-64. PMID: 28931220

83. Ciccacci C, Di Fusco D, Marazzi MC, et al. Association between CYP2B6 polymorphisms and Nevirapine-induced SJS/TEN: a pharmacogenetics study. *Eur J Clin Pharmacol.* 2013;69(11):1909-16. PMID: 23774940

84. Oluka MN, Okalebo FA, Guantai AN, et al. Cytochrome P450 2B6 genetic variants are associated with plasma nevirapine levels and clinical response in HIV-1 infected Kenyan women: a prospective cohort study. *AIDS Res Ther.* 2015;12:10. PMID: 25878720

85. Lu Y, Fuchs EJ, Hendrix CW, et al. CYP3A5 genotype impacts maraviroc concentrations in healthy volunteers. *Drug Metab Dispos.* 2014;42:1796-802. PMID: 25117426

86. Poole RM. Eliglustat: first global approval. *Drugs.* 2014;74(15):1829-36. PMID: 25239269

87. U.S. Food and Drug Administation (FDA) Center for Drug Evaluation and Research: Cerdelga/Eliglustat Tartrate. [cited 03/19/2024]. 'Available from:' http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000SumR.pdf.

88. TEC Assessment 2008. "Pharmacogenomics-based treatment of Helicobacter pylori infection." BlueCross BlueShield Association Technology Evaluation Center, Vol. 23, Tab 2.

89. Tang HL, Li Y, Hu YF, et al. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. *PLoS One.* 2013;8:e62162. PMID: 23646118

90. Morino Y, Sugimoto M, Nagata N, et al. Influence of Cytochrome P450 2C19 Genotype on Helicobacter pylori Proton Pump Inhibitor-Amoxicillin-Clarithromycin Eradication

Therapy: A Meta-Analysis. *Frontiers in pharmacology.* 2021;12:759249. PMID: 34721043

91.   Choi YJ, Lee YC, Kim JM, et al. Triple Therapy-Based on Tegoprazan, a New Potassium-Competitive Acid Blocker, for First-Line Treatment of Helicobacter pylori Infection: A Randomized, Double-Blind, Phase III, Clinical Trial. *Gut Liver.* 2022;16(4):535-46. PMID: 35791797

92.   Furuta T, Shirai N, Kodaira M, et al. Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of H. pylori. *Clin Pharmacol Ther.* 2007;81(4):521-8. PMID: 17215846

93.   Zhou L, Zhang J, Song Z, et al. Tailored versus Triple plus Bismuth or Concomitant Therapy as Initial Helicobacter pylori Treatment: A Randomized Trial. *Helicobacter.* 2016;21(2):91-9. PMID: 26104022

94.   Arevalo Galvis A, Trespalacios Rangel AA, Otero Regino W. Personalized therapy for Helicobacter pylori: CYP2C19 genotype effect on first-line triple therapy. *Helicobacter.* 2019:e12574. PMID: 30859680

95.   Kuo CH, Wang SS, Hsu WH, et al. Rabeprazole can overcome the impact of CYP2C19 polymorphism on quadruple therapy. *Helicobacter.* 2010;15(4):265-72. PMID: 20633187

96.   Zhang L, Mei Q, Li QS, et al. The effect of cytochrome P2C19 and interleukin-1 polymorphisms on H. pylori eradication rate of 1-week triple therapy with omeprazole or rabeprazole, amoxycillin and clarithromycin in Chinese people. *J Clin Pharm Ther.* 2010;35(6):713-22. PMID: 21054464

97.   Lin YA, Wang H, Gu ZJ, et al. Effect of CYP2C19 Gene Polymorphisms on Proton Pump Inhibitor, Amoxicillin, and Levofloxacin Triple Therapy for Eradication of Helicobacter Pylori. *Medical science monitor : international medical journal of experimental and clinical research.* 2017;23:2701-07. PMID: 28577017

98.   Shimoyama T, Chinda D, Sawada Y, et al. Randomized Trial Comparing Esomeprazole and Rabeprazole in First-line Eradication Therapy for Helicobacter pylori Infection based on the Serum Levels of Pepsinogens. *Internal medicine (Tokyo, Japan).* 2017;56(13):1621-27. PMID: 28674348

99.   Karaca RO, Kalkisim S, Altinbas A, et al. Effects of Genetic Polymorphisms of Cytochrome P450 Enzymes and MDR1 Transporter on Pantoprazole Metabolism and Helicobacter pylori Eradication. *Basic & clinical pharmacology & toxicology.* 2017;120(2):199-206. PMID: 27611887

100.   Nabinger DD, Mazzoleni LE, Sander GB, et al. Influence of CYP2C19 on Helicobacter pylori eradication in Brazilian patients with functional dyspepsia. *Genetics and molecular research : GMR.* 2016;15(3). PMID: 27706745

101.   Ormeci A, Emrence Z, Baran B, et al. Effect of cytochrome P450 2C19 polymorphisms on the Helicobacter pylori eradication rate following two-week triple therapy with pantoprazole or rabeprazole. *European review for medical and pharmacological sciences.* 2016;20(5):879-85. PMID: 27010145

102.   Yoshizawa Y, Sugimoto M, Sato Y, et al. Factors associated with healing of artificial ulcer after endoscopic submucosal dissection with reference to Helicobacter pylori infection, CYP2C19 genotype, and tumor location: Multicenter randomized trial. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society.* 2016;28(2):162-72. PMID: 26331711

103.   Yang JC, Wang HL, Chern HD, et al. Role of Omeprazole Dosage and Cytochrome P450 2C19 Genotype in Patients Receiving Omeprazole-Amoxicillin Dual Therapy for Helicobacter pylori Eradication. *Pharmacotherapy.* 2011;31(3):227-38. PMID: 21361732

104. Miehlke S, Lobe S, Madisch A, et al. Intragastric acidity during administration of generic omeprazole or esomeprazole - a randomised, two-way crossover study including CYP2C19 genotyping. *Aliment Pharmacol Ther.* 2011;33(4):471-6. PMID: 21175704

105. Jinda S, Nakatani K, Nishioka J, et al. Personalized treatment in the eradication therapy for Helicobacter pylori. *Int J Mol Med.* 2011;27(2):255-61. PMID: 21132257

106. Pan X, Li Y, Qiu Y, et al. Efficacy and tolerability of first-line triple therapy with levofloxacin and amoxicillin plus esomeprazole or rabeprazole for the eradication of Helicobacter pylori infection and the effect of CYP2C19 genotype: a 1-week, randomized, open-label study in Chinese adults. *Clin Ther.* 2010;32(12):2003-11. PMID: 21118735

107. Kinoshita Y, Ashida K, Hongo M. Randomised clinical trial: a multicentre, double-blind, placebo-controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. *Aliment Pharmacol Ther.* 2011;33(2):213-24. PMID: 21083596

108. Furuta K, Adachi K, Ohara S, et al. Relationship between the acid-inhibitory effects of two proton pump inhibitors and CYP2C19 genotype in Japanese subjects: a randomized two-way crossover study. *J Int Med Res.* 2010;38(4):1473-83. PMID: 20926021

109. Lee VW, Chau TS, Chan AK, et al. Pharmacogenetics of esomeprazole or rabeprazole-based triple therapy in Helicobacter pylori eradication in Hong Kong non-ulcer dyspepsia Chinese subjects. *J Clin Pharm Ther.* 2010;35(3):343-50. PMID: 20831535

110. Lee JH, Jung HY, Choi KD, et al. The Influence of CYP2C19 Polymorphism on Eradication of Helicobacter pylori: A Prospective Randomized Study of Lansoprazole and Rabeprazole. *Gut Liver.* 2010;4(2):201-6. PMID: 20559522

111. Lay CS, Lin CJ. Correlation of CYP2C19 genetic polymorphisms with helicobacter pylori eradication in patients with cirrhosis and peptic ulcer. *J Chin Med Assoc.* 2010;73(4):188-93. PMID: 20457439

112. Gawronska-Szklarz B, Siuda A, Kurzawski M, et al. Effects of CYP2C19, MDR1, and interleukin 1-B gene variants on the eradication rate of Helicobacter pylori infection by triple therapy with pantoprazole, amoxicillin, and metronidazole. *Eur J Clin Pharmacol.* 2010;66(7):681-7. PMID: 20376628

113. Serrano DR, Torrado S, Torrado-Santiago S, et al. The influence of CYP2C19 genetic polymorphism on the pharmacokinetics/pharmacodynamics of proton pump inhibitor-containing Helicobacter pylori treatments. *Curr Drug Metab.* 2012. PMID: 22493986

114. Liou JM, Chen CC, Chen MJ, et al. Empirical modified sequential therapy containing levofloxacin and high-dose esomeprazole in second-line therapy for Helicobacter pylori infection: a multicentre clinical trial. *The Journal of antimicrobial chemotherapy.* 2011;66(8):1847-52. PMID: 21632579

115. Mourad M, Wallemacq P, De Meyer M, et al. Biotransformation enzymes and drug transporters pharmacogenetics in relation to immunosuppressive drugs: impact on pharmacokinetics and clinical outcome. *Transplantation.* 2008;85(7 Suppl):S19-24. PMID: 18401258

116. MacPhee IA, Holt DW. A pharmacogenetic strategy for immunosuppression based on the CYP3A5 genotype. *Transplantation.* 2008;85(2):163-5. PMID: 18212618

117. Zhao W, Elie V, Roussey G, et al. Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. *Clin Pharmacol Ther.* 2009;86(6):609-18. PMID: 19865079

118. Han N, Yun HY, Hong JY, et al. Prediction of the tacrolimus population pharmacokinetic parameters according to CYP3A5 genotype and clinical factors using NONMEM in adult kidney transplant recipients. *Eur J Clin Pharmacol.* 2013;69(1):53-63. PMID: 22660440

119. Yang H, Sun Y, Yu X, et al. Clinical Impact of the Adaptation of Initial Tacrolimus Dosing to the CYP3A5 Genotype After Kidney Transplantation: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical pharmacokinetics.* 2021;60(7):877-85. PMID: 33751414

120. Hendijani F, Azarpira N, Kaviani M. Effect of CYP3A5*1 expression on tacrolimus required dose for transplant pediatrics: A systematic review and meta-analysis. *Pediatric transplantation.* 2018:e13248. PMID: 29920880

121. Rojas L, Neumann I, Herrero MJ, et al. Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies. *The pharmacogenomics journal.* 2015;15:38-48. PMID: 25201288

122. Khan AR, Raza A, Firasat S, et al. CYP3A5 gene polymorphisms and their impact on dosage and trough concentration of tacrolimus among kidney transplant patients: a systematic review and meta-analysis. *The pharmacogenomics journal.* 2020. PMID: 31902947

123. Rojas LE, Herrero MJ, Boso V, et al. Meta-analysis and systematic review of the effect of the donor and recipient CYP3A5 6986A>G genotype on tacrolimus dose requirements in liver transplantation. *Pharmacogenetics and genomics.* 2013;23(10):509-17. PMID: 23873120

124. Buendia JA, Bramuglia G, Staatz CE. Effects of combinational CYP3A5 6986A>G polymorphism in graft liver and native intestine on the pharmacokinetics of tacrolimus in liver transplant patients: a meta-analysis. *Ther Drug Monit.* 2014;36(4):442-7. PMID: 24378577

125. Thervet E, Loriot MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. *Clin Pharmacol Ther.* 2010;87(6):721-6. PMID: 20393454

126. Min S, Papaz T, Lafreniere-Roula M, et al. A randomized clinical trial of age and genotype-guided tacrolimus dosing after pediatric solid organ transplantation. *Pediatric transplantation.* 2018;22(7):e13285. PMID: 30178515

127. Passey C, Birnbaum AK, Brundage RC, et al. Dosing equation for tacrolimus using genetic variants and clinical factors. *British journal of clinical pharmacology.* 2011;72(6):948-57. PMID: 21671989

128. Woillard JB, Mourad M, Neely M, et al. Tacrolimus Updated Guidelines through popPK Modeling: How to Benefit More from CYP3A Pre-emptive Genotyping Prior to Kidney Transplantation. *Frontiers in pharmacology.* 2017;8:358. PMID: 28642710

129. Boughton O, Borgulya G, Cecconi M, et al. A published pharmacogenetic algorithm was poorly predictive of tacrolimus clearance in an independent cohort of renal transplant recipients. *British journal of clinical pharmacology.* 2013;76(3):425-31. PMID: 23305195

130. Tapirdamaz O, Hesselink DA, el Bouazzaoui S, et al. Genetic variance in ABCB1 and CYP3A5 does not contribute toward the development of chronic kidney disease after liver transplantation. *Pharmacogenetics and genomics.* 2014;24(9):427-35. PMID: 25014506

131. Uesugi M, Kikuchi M, Shinke H, et al. Impact of cytochrome P450 3A5 polymorphism in graft livers on the frequency of acute cellular rejection in living-donor liver transplantation. *Pharmacogenetics and genomics.* 2014;24:356-66. PMID: 24911663

132. Kato H, Usui M, Muraki Y, et al. Long-Term Influence of CYP3A5 Gene Polymorphism on Pharmacokinetics of Tacrolimus and Patient Outcome After Living Donor Liver Transplantation. *Transplantation proceedings.* 2016;48(4):1087-94. PMID: 27320564

133. Almoguera B, Riveiro-Alvarez R, Lopez-Castroman J, et al. CYP2D6 poor metabolizer status might be associated with better response to risperidone treatment. *Pharmacogenetics and genomics.* 2013;23(11):627-30. PMID: 24026091

134. Systematic Reviews on Selected Pharmacogenetic Tests for Cancer Treatment: CYP2D6 for Tamoxifen in Breast Cancer, KRAS for anti-EGFR antibodies in Colorectal Cancer, and BCR-ABL1 for Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia. 2010 [cited 03/19/2024]. 'Available from:' http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id76TA.pdf.

135. Ouvry P, Allaert FA, Desnos P, et al. Efficacy of polidocanol foam versus liquid in sclerotherapy of the great saphenous vein: a multicentre randomised controlled trial with a 2-year follow-up. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery.* 2008;36(3):366-70. PMID: 18524643

136. Province MA, Goetz MP, Brauch H, et al. CYP2D6 genotype and adjuvant tamoxifen: meta-analysis of heterogeneous study populations. *Clin Pharmacol Ther.* 2014;95:216-27. PMID: 24060820

137. Drögemöller BI, Wright GEB, Shih J, et al. CYP2D6 as a treatment decision aid for ER-positive non-metastatic breast cancer patients: a systematic review with accompanying clinical practice guidelines. *Breast Cancer Res Treat.* 2019;173(3):521-32. PMID: 30411242

138. Lu J, Li H, Guo P, et al. The effect of CYP2D6 *10 polymorphism on adjuvant tamoxifen in Asian breast cancer patients: a meta-analysis. *OncoTargets and therapy.* 2017;10:5429-37. PMID: 29180876

139. Tamura K, Imamura CK, Takano T, et al. CYP2D6 Genotype-Guided Tamoxifen Dosing in Hormone Receptor-Positive Metastatic Breast Cancer (TARGET-1): A Randomized, Open-Label, Phase II Study. *J Clin Oncol.* 2020;38(6):558-66. PMID: 31821071

140. Schroth W, Hamann U, Fasching PA, et al. CYP2D6 polymorphisms as predictors of outcome in breast cancer patients treated with tamoxifen: expanded polymorphism coverage improves risk stratification. *Clin Cancer Res.* 2010;16(17):4468-77. PMID: 20515869

141. Serrano D, Lazzeroni M, Zambon CF, et al. Efficacy of tamoxifen based on cytochrome P450 2D6, CYP2C19 and SULT1A1 genotype in the Italian Tamoxifen Prevention Trial. *The pharmacogenomics journal.* 2011;11(2):100-7. PMID: 20309015

142. Schroth W, Goetz MP, Hamann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA : the journal of the American Medical Association.* 2009;302(13):1429-36. PMID: 19809024

143. Thompson AM, Johnson A, Quinlan P, et al. Comprehensive CYP2D6 genotype and adherence affect outcome in breast cancer patients treated with tamoxifen monotherapy. *Breast Cancer Res Treat.* 2011;125(1):279-87. PMID: 20809362

144. Kiyotani K, Mushiroda T, Imamura CK, et al. Significant effect of polymorphisms in CYP2D6 and ABCC2 on clinical outcomes of adjuvant tamoxifen therapy for breast cancer patients. *J Clin Oncol.* 2010;28(8):1287-93. PMID: 20124171

145. Ramon y Cajal T, Altes A, Pare L, et al. Impact of CYP2D6 polymorphisms in tamoxifen adjuvant breast cancer treatment. *Breast Cancer Res Treat.* 2010;119(1):33-8. PMID: 19189210

146. Teh LK, Mohamed NI, Salleh MZ, et al. The risk of recurrence in breast cancer patients treated with tamoxifen: polymorphisms of CYP2D6 and ABCB1. *AAPS J.* 2012;14(1):52-9. PMID: 22183189

147. Lorizio W, Rugo H, Beattie MS, et al. Pharmacogenetic testing affects choice of therapy among women considering tamoxifen treatment. *Genome Med.* 2011;3(10):64. PMID: 21970596

148. van Schaik RH, Kok M, Sweep FC, et al. The CYP2C19*2 genotype predicts tamoxifen treatment outcome in advanced breast cancer patients. *Pharmacogenomics.* 2011;12(8):1137-46. PMID: 21830868

149. Irvin WJ, Jr., Walko CM, Weck KE, et al. Genotype-guided tamoxifen dosing increases active metabolite exposure in women with reduced CYP2D6 metabolism: a multicenter study. *J Clin Oncol.* 2011;29(24):3232-9. PMID: 21768473

150. Barginear MF, Jaremko M, Peter I, et al. Increasing tamoxifen dose in breast cancer patients based on CYP2D6 genotypes and endoxifen levels: effect on active metabolite isomers and the antiestrogenic activity score. *Clin Pharmacol Ther.* 2011;90(4):605-11. PMID: 21900890

151. Damodaran SE, Pradhan SC, Umamaheswaran G, et al. Genetic polymorphisms of CYP2D6 increase the risk for recurrence of breast cancer in patients receiving tamoxifen as an adjuvant therapy. *Cancer chemotherapy and pharmacology.* 2012;70(1):75-81. PMID: 22623212

152. Madlensky L, Natarajan L, Tchu S, et al. Tamoxifen metabolite concentrations, CYP2D6 genotype, and breast cancer outcomes. *Clin Pharmacol Ther.* 2011;89(5):718-25. PMID: 21430657

153. Park IH, Ro J, Park S, et al. Lack of any association between functionally significant CYP2D6 polymorphisms and clinical outcomes in early breast cancer patients receiving adjuvant tamoxifen treatment. *Breast Cancer Res Treat.* 2012;131(2):455-61. PMID: 21437611

154. Regan MM, Leyland-Jones B, Bouzyk M, et al. CYP2D6 Genotype and Tamoxifen Response in Postmenopausal Women with Endocrine-Responsive Breast Cancer: The Breast International Group 1-98 Trial. *J Natl Cancer Inst.* 2012;104(6):441-51. PMID: 22395644

155. Rae JM, Drury S, Hayes DF, et al. CYP2D6 and UGT2B7 Genotype and Risk of Recurrence in Tamoxifen-Treated Breast Cancer Patients. *J Natl Cancer Inst.* 2012;104(6):452-60. PMID: 22395643

156. Goetz MP, Schaid DJ, Wickerham DL, et al. Evaluation of CYP2D6 and efficacy of tamoxifen and raloxifene in women treated for breast cancer chemoprevention: results from the NSABP P1 and P2 clinical trials. *Clin Cancer Res.* 2011;17(21):6944-51. PMID: 21880792

157. Morrow PK, Serna R, Broglio K, et al. Effect of CYP2D6 polymorphisms on breast cancer recurrence. *Cancer.* 2012;118(5):1221-7. PMID: 21823108

158. Martinez de Duenas E, Ochoa Aranda E, Blancas Lopez-Barajas I, et al. Adjusting the dose of tamoxifen in patients with early breast cancer and CYP2D6 poor metabolizer phenotype. *Breast.* 2014;23(4):400-6. PMID: 24685597

159. Martins DM, Vidal FC, Souza RD, et al. Determination of CYP2D6 *3, *4, and *10 frequency in women with breast cancer in Sao Luis, Brazil, and its association with prognostic factors and disease-free survival. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica [et al].* 2014;47(11):1008-15. PMID: 25296365

160. Saladores P, Murdter T, Eccles D, et al. Tamoxifen metabolism predicts drug concentrations and outcome in premenopausal patients with early breast cancer. *The pharmacogenomics journal.* 2015;15:84-94. PMID: 25091503

161. Hertz DL, Kidwell KM, Hilsenbeck SG, et al. CYP2D6 genotype is not associated with survival in breast cancer patients treated with tamoxifen: results from a population-based study. *Breast Cancer Res Treat.* 2017;166(1):277-87. PMID: 28730340

162. Sanchez-Spitman A, Dezentje V, Swen J, et al. Tamoxifen Pharmacogenetics and Metabolism: Results From the Prospective CYPTAM Study. *J Clin Oncol.* 2019;37(8):636-46. PMID: 30676859

163. Ismail Al-Khalil W, Al-Salhi L, Rijjal S, et al. The frequencies of CYP2D6 alleles and their impact on clinical outcomes of adjuvant tamoxifen therapy in Syrian breast cancer patients. *BMC Cancer.* 2022;22(1):1067. PMID: 36243690

164. Goetz MP, Suman VJ, Hoskin TL, et al. CYP2D6 metabolism and patient outcome in the Austrian Breast and Colorectal Cancer Study Group trial (ABCSG) 8. *Clin Cancer Res.* 2013;19(2):500-7. PMID: 23213055

165. Goetz MP, Ratain M, Ingle JN. Providing Balance in ASCO Clinical Practice Guidelines: CYP2D6 Genotyping and Tamoxifen Efficacy. *J Clin Oncol.* 2016;34(32):3944-45. PMID: 27551126

166. Mehanna R, Hunter C, Davidson A, et al. Analysis of CYP2D6 genotype and response to tetrabenazine. *Movement disorders : official journal of the Movement Disorder Society.* 2013;28(2):210-5. PMID: 23280482

167. Xenazine-FDA [cited 03/19/2024]. 'Available from:' https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021894s005lbl.pdf.

168. FDA Label for Mayzent (siponimod). [cited 3/19/2024]. 'Available from:' https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209884s000lbl.pdf.

169. Locatelli I, Kastelic M, Koprivsek J, et al. A population pharmacokinetic evaluation of the influence of CYP2D6 genotype on risperidone metabolism in patients with acute episode of schizophrenia. *Eur J Pharm Sci.* 2010;41(2):289-98. PMID: 20599499

170. Wang D, Yong L, Zhang Q, et al. Impact of CYP2C19 gene polymorphisms on warfarin dose requirement: a systematic review and meta-analysis. *Pharmacogenomics.* 2022;23(16):903-11. PMID: 36222113

171. Washington HCA: Pharmacogenetic Testing for Patients Treated with Anticoagulants. [cited 3/19/2024]. 'Available from:' https://www.hca.wa.gov/assets/program/pharmacogenetics-anticoagulants-final-rpt-20180418.pdf.

172. Yang T, Zhou Y, Chen C, et al. Genotype-guided dosing versus conventional dosing of warfarin: A meta-analysis of 15 randomized controlled trials. *J Clin Pharm Ther.* 2019;44(2):197-208. PMID: 30593674

173. Sridharan K, Sivaramakrishnan G. A network meta-analysis of CYP2C9, CYP2C9 with VKORC1 and CYP2C9 with VKORC1 and CYP4F2 genotype-based warfarin dosing strategies compared to traditional. *J Clin Pharm Ther.* 2020. PMID: 33346393

174. Tse G, Gong M, Li G, et al. Genotype-guided warfarin dosing vs. conventional dosing strategies: a systematic review and meta-analysis of randomized controlled trials. *British journal of clinical pharmacology.* 2018;84(9):1868-82. PMID: 29704269

175. Kheiri B, Abdalla A, Haykal T, et al. Meta-Analysis of Genotype-Guided Versus Standard Dosing of Vitamin K Antagonists. *Am J Cardiol.* 2018;121(7):879-87. PMID: 29402419

176. Stergiopoulos K, Brown DL. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. *JAMA Intern Med.* 2014;174:1330-8. PMID: 24935087

177. Franchini M, Mengoli C, Cruciani M, et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. *Journal of thrombosis and haemostasis : JTH.* 2014;12(9):1480-7. PMID: 25040440

178. Goulding R, Dawes D, Price M, et al. Genotype-guided Drug Prescribing: A Systematic Review and Meta-analysis of Randomized Control Trials. *British journal of clinical pharmacology.* 2014. PMID: 25060532

179. Liao Z, Feng S, Ling P, et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. *Journal of thrombosis and thrombolysis.* 2015;39(2):228-34. PMID: 24962733

180. Xu H, Xie X, Wang B, et al. Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. *International journal of cardiology.* 2014;177(2):654-7. PMID: 25449474

181. Belley-Cote EP, Hanif H, D'Aragon F, et al. Genotype-guided versus standard vitamin K antagonist dosing algorithms in patients initiating anticoagulation. A systematic review and meta-analysis. *Thrombosis and haemostasis.* 2015;114(4):768-77. PMID: 26158747

182. Jonas DE, Evans JP, McLeod HL, et al. Impact of genotype-guided dosing on anticoagulation visits for adults starting warfarin: a randomized controlled trial. *Pharmacogenomics.* 2013;14(13):1593-603. PMID: 24088130

183. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med.* 2013;369(24):2294-303. PMID: 24251363

184. Hillman MA, Wilke RA, Yale SH, et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. *Clin Med Res.* 2005;3:137-45. PMID: 16160068

185. Anderson JL, Horne BD, Stevens SM, et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation.* 2007;116(22):2563-70. PMID: 17989110

186. Burmester JK, Berg RL, Yale SH, et al. A randomized controlled trial of genotype-based Coumadin initiation. *Genet Med.* 2011;13(6):509-18. PMID: 21423021

187. Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. *Clin Pharmacol Ther.* 2008;83:460-70. PMID: 17851566

188. Borgman MP, Pendleton RC, McMillin GA, et al. Prospective pilot trial of PerMIT versus standard anticoagulation service management of patients initiating oral anticoagulation. *Thrombosis and haemostasis.* 2012;108:561-9. PMID: 22836303

189. Verhoef TI, Ragia G, de Boer A, et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. *N Engl J Med.* 2013;369(24):2304-12. PMID: 24251360

190. Huang SW, Chen HS, Wang XQ, et al. Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: a prospective study in Chinese patients. *Pharmacogenetics and genomics.* 2009;19(3):226-34. PMID: 19177029

191. Zhang J, Tian L, Huang J, et al. Cytochrome P450 2C9 gene polymorphism and warfarin maintenance dosage in pediatric patients: A systematic review and meta-analysis. *Cardiovascular therapeutics.* 2017;35(1):26-32. PMID: 27661060

192. Agency for Healthcare Research and Quality (AHRQ) Technology Assessments. Reviews of Selected Pharmacogenetic Tests for Non-Cancer and Cancer Conditions. [cited 03/19/2024]. 'Available from:' http://www.cms.gov/determinationprocess/downloads/id61TA.pdf.

193. McClain MR, Palomaki GE, Piper M, et al. A rapid-ACCE review of CYP2C9 and VKORC1 alleles testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. *Genet Med.* 2008;10(2):89-98. PMID: 18281915

194. Jorgensen AL, FitzGerald RJ, Oyee J, et al. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. *PLoS One.* 2012;7(8):e44064. PMID: 22952875

195. Liang R, Wang C, Zhao H, et al. Influence of CYP4F2 genotype on warfarin dose requirement-a systematic review and meta-analysis. *Thrombosis research.* 2012;130(1):38-44. PMID: 22192158

196. Zhu Y, Xu C, Liu J. Randomized controlled trial of genotype-guided warfarin anticoagulation in Chinese elderly patients with nonvalvular atrial fibrillation. *J Clin Pharm Ther.* 2020;45(6):1466-73. PMID: 32710457

197. Stack G, Maurice CB. Warfarin Pharmacogenetics Reevaluated: Subgroup Analysis Reveals a Likely Underestimation of the Maximum Pharmacogenetic Benefit by Clinical Trials. *American journal of clinical pathology.* 2016;145(5):671-86. PMID: 27247371

198. McMillin GA, Melis R, Wilson A, et al. Gene-based warfarin dosing compared with standard of care practices in an orthopedic surgery population: a prospective, parallel cohort study. *Ther Drug Monit.* 2010;32(3):338-45. PMID: 20386359

199. Epstein RS, Moyer TP, Aubert RE, et al. Warfarin genotyping reduces hospitalization rates results from the MM-WES (Medco-Mayo Warfarin Effectiveness study). *Journal of the American College of Cardiology.* 2010;55(25):2804-12. PMID: 20381283

200. Ferder NS, Eby CS, Deych E, et al. Ability of VKORC1 and CYP2C9 to predict therapeutic warfarin dose during the initial weeks of therapy. *Journal of thrombosis and haemostasis : JTH.* 2010;8(1):95-100. PMID: 19874474

201. Moreau C, Pautas E, Gouin-Thibault I, et al. Predicting the warfarin maintenance dose in elderly inpatients at treatment initiation: accuracy of dosing algorithms incorporating or not VKORC1/CYP2C9 genotypes. *Journal of thrombosis and haemostasis : JTH.* 2011;9(4):711-8. PMID: 21255252

202. Gong IY, Tirona RG, Schwarz UI, et al. Prospective evaluation of a pharmacogenetics-guided warfarin loading and maintenance dose regimen for initiation of therapy. *Blood.* 2011;118(11):3163-71. PMID: 21725053

203. Cavallari LH, Momary KM, Patel SR, et al. Pharmacogenomics of warfarin dose requirements in Hispanics. *Blood Cells Mol Dis.* 2011;46(2):147-50. PMID: 21185752

204. Gan GG, Phipps ME, Lee MM, et al. Contribution of VKORC1 and CYP2C9 polymorphisms in the interethnic variability of warfarin dose in Malaysian populations. *Ann Hematol.* 2011;90(6):635-41. PMID: 21110192

205. Perera MA, Gamazon E, Cavallari LH, et al. The missing association: sequencing-based discovery of novel SNPs in VKORC1 and CYP2C9 that affect warfarin dose in African Americans. *Clin Pharmacol Ther.* 2011;89(3):408-15. PMID: 21270790

206. Sangviroon A, Panomvana D, Tassaneeyakul W, et al. Pharmacokinetic and pharmacodynamic variation associated with VKORC1 and CYP2C9 polymorphisms in Thai patients taking warfarin. *Drug Metab Pharmacokinet.* 2010;25(6):531-8. PMID: 20930419

207. Shahin MH, Khalifa SI, Gong Y, et al. Genetic and nongenetic factors associated with warfarin dose requirements in Egyptian patients. *Pharmacogenetics and genomics.* 2011;21(3):130-5. PMID: 21228733

208. You JH, Wong RS, Waye MM, et al. Warfarin dosing algorithm using clinical, demographic and pharmacogenetic data from Chinese patients. *Journal of thrombosis and thrombolysis.* 2011;31(1):113-8. PMID: 20585834

209. Aomori T, Obayashi K, Fujita Y, et al. Influence of CYP2C9 and vitamin k oxide reductase complex (VKORC)1 polymorphisms on time to determine the warfarin maintenance dose. *Pharmazie.* 2011;66(3):222-5. PMID: 21553655

210. Hamberg AK, Wadelius M. Pharmacogenetics-based warfarin dosing in children. *Pharmacogenomics.* 2014;15(3):361-74. PMID: 24533715

211. Hawcutt DB, Ghani AA, Sutton L, et al. Pharmacogenetics of warfarin in a paediatric population: time in therapeutic range, initial and stable dosing and adverse effects. *The pharmacogenomics journal.* 2014;14:542-8. PMID: 25001883

212. Vear SI, Ayers GD, Van Driest SL, et al. The impact of age and CYP2C9 and VKORC1 variants on stable warfarin dose in the paediatric population. *British journal of haematology.* 2014;165(6):832-5. PMID: 24601977

213. Holmes DR, Jr., Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Journal of the American College of Cardiology.* 2010;56(4):321-41. PMID: 20633831

214. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Breast Cancer. v1.2024. [cited 02/16/2024]. 'Available from:' http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

215. Harris LN, Ismaila N, McShane LM, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2016;34(10):1134-50. PMID: 26858339

216. Guyatt GH, Akl EA, Crowther M, et al. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:7S-47S. PMID: 22315257

217. Flockhart DA, O'Kane D, Williams MS, et al. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. *Genet Med.* 2008;10(2):139-50. PMID: 18281922

CODES

Codes	Number	Description
CPT	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)

Codes	Number	Description
	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)
	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)
	0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
	0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
	0349U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions
	0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
	0380U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype
	0434U	Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes
	0438U	Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted genedrug interactions
	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)

Codes	Number	Description
	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
	81418	Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
HCPCS	G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

Date of Origin: March 2011