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Medical Policy Manual

Topic: Cytochrome p450 Genotyping

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IMPORTANT REMINDER

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

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

DESCRIPTION

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

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

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

CYP450

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

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

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

- Extensive metabolizers (EM)
    - Have two active CYP450 enzyme gene alleles, resulting in an active enzyme molecule
- Poor metabolizers (PM)
    - Lack active CYP450 enzyme gene alleles
    - May suffer more adverse events at usual doses of active drugs due to reduced metabolism and increased concentrations
    - May not respond to administered prodrugs that must be converted by CYP450 enzymes into active metabolites
- Intermediate metabolizers (IM)
    - Have one active and one inactive CYP450 enzyme gene allele
- Ultrarapid metabolizers (UM)
    - Have more than 2 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]
- Some tests are offered as in-house laboratory-developed test services. These tests do not require FDA approval.

MEDICAL POLICY CRITERIA

I. Cytochrome p450 family (CYP450) 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. Except as defined in I., CYP450 genotyping is considered **investigational** for all indications, including but not limited to medication selection and dose management for the following:

   A. Antipsychotics

   B. Anti-tuberculosis medications

   C. Atomoxetine HCl

   D. Beta Blockers

   E. Codeine

   F. Efavirenz

   G. H. pylori infection

   H. Immunosuppressant for organ transplantation

   I. Selective norepinephrine reuptake inhibitors

   J. Selective serotonin reuptake inhibitor (SSRI)

   K. Tamoxifen

   L. Tricyclic antidepressants

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

SCIENTIFIC EVIDENCE

The focus of this review is on evidence from prospective randomized controlled trials (RCTs) related to the ability of test results to 1) guide decisions in the clinical setting related to treatment, management, or prevention; and 2) improve health outcomes as a result of those decisions.

The following limitations in the current evidence were noted:

- The available evidence is not sufficient to establish how CYP450 genotyping improves patient management with respect to drug selection and dosing compared to standard treatment without genotyping.
- It is not known if genotyping improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate.
- In general, most published CYP450 pharmacogenomic studies are retrospective evaluations of CYP450 genotype associations, reporting intermediate outcomes (e.g., circulating drug concentrations) or less often, final outcomes (e.g., adverse events or efficacy). Studies are mostly small and under-powered.
- There is a lack of randomized, prospective studies evaluating the clinical utility of CYP450 genotyping for any of the indications discussed below.

Antipsychotics Selection and Dosing

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

Literature Appraisal

Systematic Reviews and Meta-analysis

- In 2011, Fleeman et al. published a systematic review and meta-analyses of CYP450 testing for use in prescribing antipsychotics in adults with schizophrenia.[2] After conducting a search of 2841 publications, the authors identified 47 studies that described clinical validity, but failed to identify published studies on the clinical utility of testing. The authors found no convincing evidence of an association between test results and either drug efficacy or toxicity. When seen, differences were considered too small to be clinically meaningful (eg, an association of mutation status with tardive dyskinesia).
- In a 2013 systematic review, the pharmacogenetics of risperidone was evaluated.[3] The review identified 10 prospective nonrandomized, uncontrolled cohort studies, 1 retrospective cohort study, 1 prospective case-control study, and 1 retrospective case series. While there were trends toward increased adverse effects in poor metabolizers, most outcomes were not significant. Based on the results of the review, the authors concluded that routine genotyping should not be used for screening. Further, authors suggest that adequately powered clinical and epidemiologic studies are warranted to clarify the role of CYP2D6 genotyping in practice.

Nonrandomized Studies

The evidence is limited to small, nonrandomized and/or retrospective studies of antipsychotics and CYP450 metabolism. No prospective trials of genotype-directed antipsychotic selection or dosing have been reported.[4-7] Prospective randomized controlled clinical trials are needed to determine the independent contribution of CYP450 on both initial dosing and therapeutic drug monitoring.

Clinical Practice Guidelines

Currently no published clinical practice guidelines recommend CYP450 genetic testing for the selection and dosing of antipsychotics**.**

Conclusions: Individuals with genetic variants in the CYPD6 gene may be at increased risk for adverse effects of antipsychotic drugs, particularly extrapyramidal effects such as tardive dyskinesia and pimozide-induced arrhythmias. However, the clinical utility of testing is uncertain, since management changes as a result of genetic testing have not been evaluated.

Anti-tuberculosis Medications

Literature Appraisal

A number of studies have reported an association between CYP2E1 status and the risk of liver toxicity from anti-tuberculosis medications.

Meta-analyses

- A meta-analysis of available trials was reported by Deng et al. in 2013. Compared with wild type genotype, patients with any variant genotype had an increased risk of liver toxicity (OR 1.36, 95% CI 1.09-1.69).[8] Patients who were slow metabolizers had the highest risk of toxicity (OR 1.88, 95% CI 1.14-3.09), and this overall risk was also increased in Asian patients. This study does not address the question of whether genetic testing can reduce liver damage from anti-tuberculosis medications, compared to the usual strategy of monitoring liver enzymes and adjusting medications based on enzyme levels.
- In a second meta-analysis, Sheng and others investigated the potential association between cytochrome P450 2E1 (CYP2E1) polymorphisms and the risk of anti-tuberculosis drug-induced hepatotoxicity (ATDH).[9] Compared with the wild genotype (c1/c1), the odds ratio (OR) of ATDH was 1.41 (95% CI: 1.1-1.82, P=0.007) for the PstI/RsaI polymorphism, and 0.78 (95% CI: 0.51-1.18, P=0.23) for the DraI polymorphism. Compared with individuals with N-acetyltransferase 2 (NAT2) fast or intermediate acetylator genotype and c1/c1 genotype patients who were NAT2 slow acetylators and carried the high activity CYP2E1 c1/c1 genotype had higher risk for ATDH (OR=3.10, P<0.0001). Authors concluded the meta-analysis indicated that the CYP2E1 c1/c1 genotype may be a risk factor for ATDH.

Clinical Practice Guidelines

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

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

Beta Blocker Selection and Dosing

Literature Appraisal

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

Nonrandomized Studies

Existing studies have reported contradictory findings concerning the association of the CYP2D6 genotype and the response to beta blockers. A few studies have indicated that lipophilic beta selective adrenergic receptor antagonists, such as metoprolol used in treating hypertension, may exhibit impaired elimination in patients with CYP2D6 polymorphisms.[10,11] In addition, increased risk of bradycardia was observed in patients found to be poor metabolizers (CYP2D6 *4/*4), although the clinical significance of this observation remains to be defined.[10] In contrast, it has also been reported that no difference in response to metoprolol or carvedilol was observed according to genotype.[12]

Clinical Practice Guidelines

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

Conclusions: The clinical utility of testing for CYP450 genotyping is uncertain, since management changes for beta-blocker medications based on genotyping results has not been evaluated.

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

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

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

Literature Appraisal

Systematic Reviews and Meta-Analyses

Two systematic reviews and meta-analyses have been published, all suggesting that CYP2C19 gene polymorphisms do not have a substantial or consistent influence on the clinical efficacy of clopidogrel:

- In 2011, Bauer et al. carried out an extensive literature review and meta-analysis of the genetic studies examining the impact of variants of the CYP2C19 genotype on the clinical efficacy of clopidogrel.[13] Out of 4,203 identified publications, 15 studies met the prespecified inclusion criteria. When comparing carriers of at least one reduced function allele of CYP2C19 with non-carriers, the unadjusted odds ratios of major adverse events were higher in 3 studies, lower in 1, and not significantly different in 8. For stent thrombosis the odds ratio associated with reduced function allele carrier status was reduced in 4 studies but showed no significant difference in 5. 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 et al. searched PubMed and EMBASE for studies linking CYP2C19 testing to treatment with clopidogrel.[14] They identified 32 studies including 42,106 participants. Twenty one studies included patients with acute coronary syndromes and 8 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 recent editorial, Beitelshees notes that the results of this analysis may have been compromised by the fact that patients who did not undergo percutaneous coronary intervention (PCI) were included.[15] 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.[16] A total of 4819 patients were genotyped in this study and no relationship between CYP2C19 status and ischemic outcomes in stable patients was observed. Bhatt also observed significantly less bleeding in this subgroup.

Randomized Controlled Trials (RCTs)

- Roberts et al. reported on the use of a point-of-care CYP2C19*C genetic test for treatment selection (standard treatment [prasugrel] versus clopidogrel).[17] In this controlled trial, patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome or stable angina were randomized to genotyping for treatment selection or standard treatment. In the tested group, carriers were given 10 mg of prasugrel daily. Non carriers and all patients in the control group were given 75 mg of clopidogrel per day. The primary endpoint was high on-treatment platelet reactivity as the primary endpoint. This measure is used as a marker of cardiovascular events. In the group with genotyping none of the 23 carriers had high on-treatment platelet reactivity; in the group receiving standard treatment 30% of 23 carriers had high on-treatment platelet reactivity. These authors concluded that rapid genotyping with subsequent personalized treatment reduces the number of carriers treated who exhibit high on-treatment reactivity. The authors do note that alternative approaches using either phenotyping or a combination of both phenotyping and genotyping might optimize treatment decision making.
- Mega et al. also reported on the use of CYP2C19 genotyping for dosing of clopidogrel and the effect on platelet reactivity in patients with stable cardiovascular disease.[18] Their findings suggest that changes in platelet reactivity in carriers may be dose dependent and that in PCI patients

heterozygous caries might require up to triple dosing of clopidogrel to reach a desired target platelet reactivity level. In homozygous carriers, even with higher clopidogrel doses, platelet reactivity cannot be raised to the level of clopidogrel treatment in non-carriers.

Nonrandomized Studies

- Nonrandomized studies have reported conflicting findings. Several nonrandomized studies found increased risks of thrombotic events in patients treated with clopidogrel who were CYP2C19 variant carriers.[19-25] However, in one large retrospective study of 5,059 patients from two large RCTs that compared clopidogrel with placebo in reducing the rate of cardiovascular events, the authors reported that that the efficacy and safety of clopidogrel as compared with placebo was not affected by CYP2C19 loss of function alleles. Even when data were restricted to evaluation of patients homozygous for loss of function, no increased risk of cardiovascular events was observed.
- Recent studies have suggested that changes in platelet reactivity in carriers may be dose-dependent and that in PCI patients, heterozygous carriers might require up to triple dosing of clopidogrel to reach a desired target platelet reactivity level.[18,26] In homozygous carriers, it has been reported that even with higher clopidogrel doses, platelet reactivity cannot be raised to the level of clopidogrel treatment in non-carriers. In these patients other drugs such as prasugrel or ticagrelor may be used as treatment alternatives.

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

In 2010, the FDA issued a public safety communication and added a boxed warning to the label of Plavix about the availability of genetic testing and alternative drug therapies in patients who are found to be poor metabolizers of the drug (patients with CYP2C19 *2/2, *3/3, or *2/3 genotypes). The FDA endorsement is based on retrospective analyses which suggested that PM status had a higher rate of cardiovascular events or stent thrombosis compared to EM.[26,27]

Clinical Practice Guidelines

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.[28] 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. The selection of the specific test, as well as the issue of reimbursement, are both important additional considerations.
- The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.
- There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance.

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

Codeine Prescription for Nursing Mothers

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

Literature Appraisal

No prospective trials of genotype-directed codeine dosing in nursing mothers have been reported.

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

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

Clinical Practice Guidelines

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

Conclusions: The relationship between genetic variants of cytochrome p450, codeine metabolism, and nursing mothers is not certain. 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.

Efavirenz Dosing for the Treatment of HIV Infection

Current guidelines recommend efavirenz as the preferred non-nucleoside reverse transcriptase inhibitor component of highly active antiretroviral therapy for HIV-infected patients. Forty to 70% of patients report adverse central nervous system effects. While most resolve in the first few weeks of treatment, about 6% of patients discontinue efavirenz due to adverse effects.[30] 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.

Literature Appraisal

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

Nonrandomized Studies

- Limited reports suggest that CYP2B6 poor metabolizers have markedly reduced side effects while maintaining viral immunosuppression at substantially lower doses.[31,32] Simulations of such dose adjustments support this position.[33] 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.
- Two recent studies have been published, one evaluating 373 patients for polymorphisms in CYP2B6 and constitutive androstane receptor (CAR)[34], and one evaluating genotyping for 23 markers in 15 genes[35]. Both demonstrated an association between markers and early efavirenz discontinuation. Both articles recommended further study to determine the clinical utility of these associations.

Clinical Practice Guidelines

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

Conclusions. 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.

H. pylori Infection[36,37]

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

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

To determine whether treatment decisions based on genetic testing improve health outcomes, direct comparisons with standard treatment selection strategies are needed. Prospective randomized controlled trials (RCTs) comparing the two strategies are necessary for reliable comparisons. The optimal trial would isolate the impact of treatment changes made as a result of genetic status, be performed in the U.S. in a population with rates of CYP2C19 polymorphisms approximating that of the general U.S. population, use an approach to diagnosing H. pylori that reflects usual care in the U.S., and would use a standard treatment regimen recommended for U.S. patients.[36]

Literature Appraisal

Technology Assessment

A 2008 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment concluded that the scientific evidence did not permit conclusions on whether the use of a pharmacogenomics-based treatment regimen for H. pylori improves eradication rates.[36]

Meta-Analysis

Tang and others performed a meta-analysis of RCTs to re-evaluate the impact of CYP2C19 variants on PPI-based triple therapy for *H. pylori* infection.[38] Authors identified 16 RCT datasets derived from 3680 patients. There were significant differences in that rate between homozygous (HomEMs) and heterozygous (HetEMs) extensive metabolizers (OR 0.724; 95% CI 0.594-0.881), between HomEMs and poor metabolizers (PM) (OR 0.507; 95%CI 0.379-0.679), or between HetEMs and PMs (OR 0.688; 95%CI 0.515-0.920), regardless of the PPI being taken. Furthermore, sub-analysis of individual PPIs was carried out to explore the difference across all the PPIs used. A significantly low rate was seen in HomEMs vs. HetEMs taking either omeprazole (OR 0.329; 95%CI 0.195-0.553) or lansoprazole (OR 0.692; 95%CI 0.485-0.988), and also in HomEMs vs. PMs for omeprazole (OR 0.232; 95%CI 0.105-0.515) or lansoprazole (OR 0.441; 95%CI 0.252-0.771). However, there was no significant difference between HetEMs and PMs taking either one. No significant differences were observed for rabeprazole or esomeprazole across the CYP2C19 genotypes of interest. Authors concluded that carriage of CYP2C19 loss-of-function variants is associated with increased *H. pylori* eradication rate in patients taking PPI-based triple therapies when omeprazole or lansoprazole is chosen. In the meta-analysis, individual PPIs were pooled without considering the dose, duration of therapy and the type of antibiotic agents, resulting in some confounders for *CYP2C19* phenotypes and the eradication rates of PPI-based therapy. Therefore, results may not be generalizable to clinical practice.

Randomized Controlled Trials (RCTs)

- A randomized, controlled trial comparing a pharmacogenomics-based treatment regimen with a standard regimen was evaluated.[39] This study randomized 300 Japanese patients to a pharmacogenomics-based treatment regimen versus a standard treatment regimen. The TEC Assessment offered the following observations and conclusions concerning this study:
    - Eradication rates after first-line treatment were higher in this study for the pharmacogenomics group compared with the standard treatment group. However, because of numerous variations in treatment protocol within the pharmacogenomics group, it was not possible to determine whether the improvement resulted from the tailored PPI dosages according to CYP2C19 genetic status, or due to other variations in the treatment protocol unrelated to CYP2C19 status.
    - There were numerous variations in the treatment regimen within the experimental group that made it difficult to determine which specific aspects of the treatment regimen may have led to benefit. In particular, it appeared that clarithromycin resistance was an important factor in treatment success, and that there may have been an interaction between clarithromycin resistance and CYP2C19 status. From the data reported in the study, it was not possible to separate the potential impact of clarithromycin resistance on eradication rates from the impact of pharmacogenetically tailored PPI dosage schedules.
    - In addition to the limitations on internal validity, the clinical relevance of the study was also limited for several reasons. The treatment approach used was relatively intensive, including genetic testing for CYP2C19, esophagogastroduodenoscopy with biopsy for all patients, and testing of H. pylori isolates for clarithromycin resistance. This treatment approach was much more intensive than that generally used in the United States, where the diagnosis of *H. pylori* is usually made by noninvasive methods, and initial empiric

treatment is instituted without isolating *H. pylori* or testing for resistance. Furthermore, the patient population was from Japan, limiting the generalizability of the results, especially given the ethnic differences in CYP2C19 genetic status.

- Additional RCTs evaluating H. *pylori* eradication rates for different treatment regimens reported that the CYP2C19 genotype appears to play a role in eradication rates.[40,41] However, these trials were not designed to compare a pharmacogenomics-based treatment regimen with a standard regimen.

Nonrandomized Studies

Additional small, nonrandomized and/or retrospective studies of CYP2C19 gene polymorphisms and H. *pylori* treatment have been published; however, the clinical utility of genotyping is not addressed. [40,42-53]

Clinical Practice Guidelines

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

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

Immunosuppressant Dosing for Organ Transplantation

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

Literature Appraisal

- Tacrolimus blood levels are related to CYP3A5 genetic variants, with an approximately 2.3-fold difference in daily dose required to maintain target concentration between CYP3A5*3 and CYP3A5*1 homozygous variants.[54]
- CYP3A5*1 carriers have been reported to have a significant delay in reaching target tacrolimus concentrations compared to non-carriers. Although the overall rate of acute rejection episodes was not higher in CYP3A5*1 carriers, their rejection episodes did occur earlier.[55]
- Population-based pharmacokinetic models for clearance of tacrolimus in kidney transplant recipients have been developed for both adult and children.[56,57] 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.

Meta-analysis

In a recent meta-analysis, Rojas and others investigated the effect of the CYP3A5 6986A>G polymorphism in liver donors and transplant recipients on tacrolimus pharmacokinetics.[58] 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.

Clinical Practice Guidelines

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

Conclusions: There is currently limited evidence on the impact of genotype on dosing on immunosuppressant medications. Clinical utility for this test is lacking at the current time.

Selective Norepinephrine Reuptake Inhibitors (SNRIs)

Antidepressants

SNRIs are used most commonly as antidepressants. Available agents in the US include venlafaxine, duloxetine, and nefazodone. All of these drugs are metabolized by the cytochrome p450 system, and medication levels vary according to cytochrome p450 status.[59] Some of these agents, for example venlafaxine, are metabolized to an active metabolite by the CYP2D6 enzyme, and other agents such as duloxetine are inhibitors of cytochrome p450 activity.

Lobello et al. tested patients from four RCTs of venlafaxine versus placebo for CYP2D6 status and correlated genetic status, defined as either extensive metabolizers (EM) or poor metabolizers (PM), with response to treatment.[60] There were no significant differences in dose of the drug according to genetic status. In 4 of 5 comparisons, patients who were EMs had a better response to treatment as determined by depression rating scales. There was also a significantly greater percent of responders in the EM group compared to the PM. There were no differences in discontinuation of therapy or adverse event rates between the EM and PM group.

For duloxetine, the inhibitory effects on cytochrome p450 activity are manifested by higher drug concentrations for other medications metabolized by cytochrome p450 such as tricyclic antidepressants and/or SSRIs. Similarly, other inhibitors of cytochrome p450 such as paroxetine, will increase levels of duloxetine.[61]

Atomoxetine HCl Dosing For the Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD)

Atomoxetine HCl is a selective norepinephrine reuptake inhibitor that is prescribed to treat ADHD. Atomoxetine HCl is primarily metabolized by CYP2D6.

The therapeutic window for atomoxetine is wide, and dosing is weight-based, initiated at a standard dose per kg and adjusted thereafter according to clinical response and adverse effects. At steady state dosing, CYP2D6 poor metabolizers have substantially higher atomoxetine plasma concentrations than normal, extensive metabolizers (EMs). However, because the drug is generally well tolerated across a wide

range, adverse effects do not appear to be significantly associated with poor metabolizers.[62,63] After titration, mean doses for EMs and poor metabolizers also do not differ significantly.[63,64] However, more EM patients discontinued in one trial due to lack of efficacy[64] and poor metabolizers improved inattention scores more than EMs in another,[63] perhaps suggesting a need to re-examine recommended dosing limits.

The FDA decided not to include a recommendation to perform genotyping prior to prescribing atomoxetine. Dosing directions recommend a low starting dose to be increased to the target dose if well tolerated. Thus, genotyping for CYP2D6 poor metabolizers of atomoxetine is not recommended because the margin of safety is not exceeded and evidence to support guidelines for dosing such that patient outcomes are improved has not been collected.[65-67]

Literature Appraisal

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

Nonrandomized Studies

- Ramoz et al. recently reported on two independent cohorts of 160 and 105 ADHD children treated for 6 weeks with atomoxetine.[67] Interindividual response to the drug appeared independent of the genetic variants of CYP2D6. The authors did observe drug treatment and genomic associations, but these were found between drug response and a haplotype of the norepinephrine transporter (NET) gene–Slc6a2. It was suggested further study be applied to assessment of this region to better manage patients being treated with this drug.
- ter Laak et al. evaluated 100 patients treated for ADHD with standard doses of atomoxetine.[68] A neurologist identified 10 of these who, based on late response or adverse effects, were subject to CYP P450 testing. Eight of the 10 were found to have a nonfunctional or less functional 2D6 allele. Four of these children showed improved responses on decreased atomoxetine; four were taken off treatment because of initial adverse events. While it is plausible that pretreatment testing could yield improved results, the study was not designed to evaluate the actual effect of testing on treatment outcomes.

Clinical Practice Guidelines

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

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

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

Selective Serotonin Reuptake Inhibitors (SSRIs) Selection and Dosing

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

Literature Appraisal

Technology Assessments

The Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) systematically reviewed the evidence on CYP450 testing for adults treated with SSRIs for nonpsychotic depression.[69] The report concluded, "The data fail to support a clear correlation between CYP polymorphisms and SSRI levels, SSRI efficacy, or tolerability. There are no data regarding whether testing leads to improved outcomes versus not testing in the treatment of depression; whether testing influences medical, personal, or public health decision making; or whether any harms are associated with testing itself or with subsequent management options."

Nonrandomized Studies

Although nonrandomized and/or retrospective studies of CYP450 and SSRIs metabolism have been published, no prospective randomized trials of genotype-directed SSRI selection or dosing have been reported yet.[70-74]

Clinical Practice Guidelines

Following this commissioned report, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group published the following recommendation: "The EGAPP Working Group found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed."[75]

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

Tamoxifen: Managing Treatment for Women at High Risk For or With Breast Cancer[76,77]

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

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

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

- Treatment of metastatic disease

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

Literature Appraisal

Technology Assessments

- 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.[78] Sixteen publications of CYP2D6 testing met the eligibility criteria and were included in the review (15 studies in the adjuvant setting and 1 study in the metastatic setting). However, the meta-analysis was not performed due to extensive heterogeneity in the definition of slow, intermediate, and extreme metabolizers across eligible studies. Instead, the results from individual studies on the strength of the association between CYP2D6 testing results and clinical outcomes were presented. The assessment concluded the following:

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

  Based on a 2008 BlueCross BlueShield Association Technology Evaluation Center Assessment, results from clinical validity studies of CYP2D6 for use in tamoxifen management are uncertain.[77] Evidence from two higher quality trials of adjuvant TAM in relatively homogeneous patient populations suggests that women treated with TAM who are functional poor metabolizers or intermediate metabolizers, whether by genotype or by co-medication with CYP2D6 inhibitors, have significantly reduced time to recurrence and recurrence-free survival (but not overall survival) compared to extensive metabolizers. The significance levels are marginal but might have been stronger and more convincing if poor metabolizers alone could have been compared to extensive metabolizers, but numbers of poor metabolizers were insufficient. Few variant alleles have been typed in these studies; more extensive genotyping and better categorization might also strengthen results.

Meta-analysis

The International Tamoxifen Pharmacogenomics Consortium was established to address the controversy regarding cytochrome P450 2D6 (CYP2D6) status and clinical outcomes in tamoxifen therapy. Authors from this consortium performed a meta-analysis on data from 4,973 tamoxifen-treated patients (12 globally distributed sites).[79]Using strict eligibility requirements (postmenopausal women with estrogen receptor-positive breast cancer, receiving 20 mg/day tamoxifen for 5 years, criterion 1); CYP2D6 poor metabolizer status was associated with poorer invasive disease-free survival (IDFS: hazard ratio = 1.25; 95% confidence interval = 1.06, 1.47; P = 0.009). However, CYP2D6 status was not statistically significant when tamoxifen duration, menopausal status,

and annual follow-up were not specified (criterion 2, n = 2,443; P = 0.25) or when no exclusions were applied (criterion 3, n = 4,935; P = 0.38). Authors concluded, although CYP2D6 is a strong predictor of IDFS using strict inclusion criteria, because the results are not robust to inclusion criteria (these were not defined a priori), prospective studies are necessary to fully establish the value of CYP2D6 genotyping in tamoxifen therapy.

Nonrandomized Studies

Although nonrandomized and/or retrospective studies have been published, no prospective randomized clinical trials have been conducted that provide *direct* evidence of the clinical utility of genotype-directed tamoxifen treatment management for women at high risk for or with breast cancer. Further, nonrandomized studies have been reporting conflicting findings regarding the role of CYP2D6 mutational status in the selection and dosing of tamoxifen, with some in support[80-92] and others not.[93-97]

Clinical Practice Guidelines

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

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

Tricyclic Antidepressants

Nortriptyline and other tricyclic antidepressants (TCA) are metabolized by the CYP2D6 enzyme. Patients who are poor metabolizers (PMs) will develop serum concentrations of nortriptylline that are 3-10 fold higher than patients who are extensive metabolizers (EM).[98]

Literature Appraisal

Nonrandomized Studies

- de Vos et al. studied 678 patients treated with TCAs and reported that EMs had increased metabolism and lower serum levels of amitriptyline and citalopram, but not clomipramine.[99] However, these authors reported that the differences observed were not likely to have clinically important effects.
- It has been reported that patients with TCA overdose may have different risk depending on cytochrome p450 genetic status.[99,100] Simulations and case reports have reported that PMs may be at higher risk for toxic levels of nortriptylline, and that toxic levels are maintained for longer periods of time. There are no clinical studies that demonstrate that measuring genetic status improves outcomes for patients who have had a TCA overdose.

Clinical Practice Guidelines

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

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

Warfarin Dosing and Management[101]

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 VKORC1genetic testing is to predict an individual's likely stable warfarin dose by incorporating demographic, clinical, and genotype data. Warfarin is then initiated at that predicted dose as a way to limit over-anticoagulation and increased risk of serious bleeding events.

Regulatory Status

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

Literature Appraisal

Technology Assessments

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).[102] The review concluded the following:

- Carriers of the CYP2C9 gene variant alleles *2 or *3 require lower mean maintenance warfarin doses than do non-carriers.
- Few studies investigated the relationship between genetic variations in CYP2C9 or VKORC1 and warfarin dose requirements in the induction phase. CYP2C9 variants were associated with an increased rate of bleeding complications during the induction phase of warfarin therapy, but the studies did not report whether affected patients had normal or supratherapeutic NR ranges.

- The clinical utility of genetic testing for CYP2C9 in everyday clinical practice is not straightforward.
- It is unclear whether dose-prediction algorithms using genetic information improve clinical outcomes over those of standard practice. Only 3 RCT addressed this question, but all had flaws in design and inclusion criteria, and had inadequate power to reach statistical conclusions.
- Carriers of the three common VKORC1 variants (alleles T, G, and C) required lower mean maintenance doses of warfarin than did non-carriers. Data were not adequate to address any other questions.

New genetic associations such as CYP4F2 are under investigation and evaluating interactions among CYP2C9, VOKRC1, and this new variant along with gene-environmental interactions may result in better risk predictive instruments for clinical use.

Systematic Reviews

- 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 has yet shown this to be acceptable or effective.[103] Several randomized trials were noted to be underway to determine the clinical utility of testing.
- Jorgensen and others investigated the influence of CYP2C9 and VKORC1 on patient response to warfarin in a 2012 systematic review and meta-analysis of 117 studies.[104] Authors concluded that genetic associations with warfarin response vary between ethnicities. In addition authors suggest that a high level of methodological rigor must be maintained and studies should report sufficient data to enable inclusion in meta-analyses and achieve unbiased estimates in different populations.
- A systematic review and meta-analysis by Liang et al. suggested a more substantial contribution of *CYP4F2* genetic variants.[105] Compared with wild type patients, carriers of *CYP4F2* variants required warfarin doses 11% and 21% higher for heterozygous and homozygous patients, respectively.

Randomized Controlled Trials (RCTs)

- In 2013, Jonas et al. conducted a double-blind, RCT in 109 adults who were initiating long-term warfarin therapy.[106] Patients were randomized to warfarin dosing by an algorithm that contained both genetic (specifically, *CYP2D6*2* and **3* and *VKORC1*-1639G>A [also known as VKORC1 3673G>A]) and clinical factors or clinical factors only. Most patients (70%) were Caucasian, and 30% were African-American. Primary efficacy outcomes were the mean number of anti-coagulation visits (to clinic or physician) in 90 days and time in the therapeutic range (TTR). The trial was powered to detect a difference of 2 visits and a 10% difference in TTR. There were no statistically significant differences between intervention groups for any primary or secondary outcome. (Secondary outcomes included emergency visits, hospitalizations, minor [not requiring hospitalization or transfusion] and major hemorrhagic events, thrombotic events and deaths, but the trial was not powered to detect differences in these outcomes.) The authors concluded, "Overall, the current evidence from our trial and from previously published trials does not establish clinical utility of genotype-guided warfarin dosing."
- The Clarification of Optimal Anticoagulation through Genetics (COAG) trial (72) compared 2 dosing algorithms in 1,015 patients who were initiating a minimum 1 month course of warfarin therapy (58% for deep vein thrombosis or pulmonary embolism, 22% for atrial fibrillation, and 11% for other indications).[107] Median patient age was 58 years (interquartile range [IQR] 46 to 70). Patients were stratified by self-reported race (black [27%] or non-black [73%]), randomized in

double-blind fashion to an algorithm of both clinical and genetic factors or clinical factors only, and followed for 4 weeks. Ninety-four percent of patients (n=955) completed the 5-day intervention period and were included in efficacy analyses. The between-group difference in the primary outcome was not statistically significant (45.2% and 45.4% of INRs were in the therapeutic range in the genotype-guided and clinically-guided groups, respectively; p=0.91). Among 255 black patients, a statistically significant difference favored the clinically-guided group (35.2% and 43.5 % of INRs were in the therapeutic range in the genotype-guided and clinically-guided groups, respectively; p=0.01). The principal secondary outcome (a composite of INR ≥4, major bleeding [fatal hemorrhage, intracranial bleeding, or symptomatic bleeding requiring overnight hospitalization, transfusion, angiographic intervention, or surgery], or thromboembolism) occurred in 20% and 21% of the genotype- and clinically-guided groups, respectively (p=0.93). Incidences of each component of the composite outcome also were similar between groups, although the trial was not powered for these outcomes.

- The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial compared algorithm-based dosing, using clinical and genetic information, to standard fixed-dose warfarin initiation (with a 10 mg loading dose on day 1) in 455 patients with atrial fibrillation (72%) or venous thromboembolism (28%).[108] Almost all patients (99%) were white. Mean patient age was 67.5 years (range 24 to 90). Patients were randomized to 1 of the 2 treatment groups and followed for 12 weeks. Ninety-four percent of patients had 13 or more days of INR data and were included in efficacy analyses. The between-group difference in the primary outcome favored genotype-guided dosing (67.4% and 60.3% of INRs were in the therapeutic range in the genotype-guided and fixed-dose groups, respectively; p<0.001). The median time to reach a therapeutic INR (a secondary outcome, calculated as the median time to the first of 2 target INR values, measured at least 1 week apart) was 21 days (IQR 8 to 36) in the genotype-guided group and 29 days (IQR 14 to 58) in the fixed-dose group (p<0.001); the percentage of time in the therapeutic range was no longer statistically different between groups after week 8. Excessive anticoagulation (INR ≥4.0) occurred in fewer patients in the genotype-guided group (27%) than in the control group (37%; p=0.03). Bleeding events occurred in approximately 38% of patients in each group, and most consisted of bruising and nosebleeds. One thromboembolic event occurred in the control group.
- One small randomized trial (not included in the ACMC review above) failed to demonstrate a beneficial impact of pharmacogenetic warfarin dosing of International Normalized Ratio (INR)-based outcomes (INR is a standardized indicator of clotting time). However, the study was relatively small (n=206) and had only intermediate power to detect small differences in the primary and secondary end points.[109]
- Burmester et al. in association with the AHRQ and Third Wave Technologies conducted a prospective, randomized, blinded, two-arm trial to determine whether initial warfarin dosing based on an algorithm using relevant genetic polymorphisms and clinical parameters (genetic and clinical arm) was superior to an algorithm using only usual clinical parameters (clinical only arm) in predicting stable therapeutic dose of warfarin and in anticoagulation outcomes.[110] A total of 230 primarily hospitalized patients were enrolled. The model including genotype predicted therapeutic dose better than the clinical-only model (p=0.0001); both models predicted dose better than the standard starting dose of 5 mg/day. However, the median percentage of time in INR range was the same at 28.6% in each arm. Observed times to stable therapeutic dose were also very similar in the 2 arms. During the trial, INR exceeded 4.0 in 35% of subjects in the clinical-only arm and in 38% of subjects in the genetic clinical arm. Thus, clinical outcomes were similar despite improved prediction with genetic information. Patients in this trial may have had frequent INR measurements and dose adjustments in a hospital setting; results may not reflect those likely to be obtained in an outpatient setting.

- A blinded, randomized clinical trial (CoumaGen-II) by Anderson et al. investigated if 2 pharmacogenetic-guided (PG) testing algorithms were better than standard empiric warfarin dosing.[111] A parallel control group (n=1,866) included patients initiating warfarin treatment during the study period, and for these patients, warfarin dose was determined by physician/health-care provider. Same day genotyping of *CYP2C9* and *VKORC1* was provided to 504 randomized patients; 257 patients in the 1-step arm (IWPC algorithm) and 247 in the 3-step arm (modified IWPC algorithm). The vast majority of patients (91.4% in the control group and 95.4% in the PG group) were of Caucasian ancestry. Primary endpoints were the percentage out-of-range of INRs and time in therapeutic range during the first month and through the third month of warfarin therapy. Both PG approaches were observed to be equivalent at 1 and 3 months for all outcomes with a stable maintenance dose determined in 444 patients. There was an inverse relation between the number of reduced function alleles and the ability to predict a stable maintenance dose ($p<0.001$). Pharmacogenomic guidance was more accurate in wild-type patients and those with multiple variants ($p<0.001$). Both PG arms were pooled and were observed to be superior to the standard dosing approach with significant ($p<0.001$) reductions in percent of time out of INR range and percentage of time in therapeutic range at 1 and 3 months after controlling for relevant variables. Adverse events (hemorrhagic events, thromboembolic events, or other serious adverse events) were greater in the control group (4.5%) compared to the PG group (9.4%), with an adjusted relative risk of .44 (95% CI: 0.28-0.70, $p<0.001$).
- A prospective, single-arm study (n=344) by Perlstein et al. assessed the validity of 3 warfarin dosing algorithms to predict time in therapeutic range and time to first therapeutic INR in a predominantly Caucasian population.[112] The dosing algorithms were developed sequentially to select both an initial warfarin dose and a titration scheme intended to maximize the likelihood of achieving and maintaining the target INR. Algorithm A determined the initial dosing with a decision tree including both clinical and genetic factors based on best practices in the hospital's anticoagulation management service and the published literature. Algorithm B was generated from an analysis of warfarin dose, INR, genetic factors, demographic factors, and concomitant drug therapy from a group of 74 patients treated with Algorithm A. Algorithm C was an update to Algorithm B, with the chief difference being a revision of the half maximal inhibitory concentration for *VKORC1* haplotypes. The authors found a significant ($p=0.04$) progressive improvement in mean percentage time in therapeutic range over the entire study period for Algorithm A (58.9), Algorithm B (59.7), and Algorithm C (65.8). The secondary endpoint of per-patient percentage of INRs outside of the therapeutic range had a similar statistically significant trend across algorithms ($p=0.004$) with Algorithm A reporting 21.6%, algorithm B 22.8%, and algorithm C 16.8%. Time to stable therapeutic anticoagulation decreased significantly across algorithms ($p<0.001$), but time to first therapeutic INR did not vary significantly among the 3 algorithm sub-groups. No differences in rates of adverse events were observed during this study.

Nonrandomized Studies

Although nonrandomized and/or retrospective studies of genotype-based vs. standard warfarin dosing have been published, evidence from these studies is unreliable due to inherent design flaws, such as non-random allocation of dosing management and lack of appropriate comparison groups.[113-124]

Clinical Practice Guidelines

- The 2012 American College of Chest Physicians evidence-based clinical practice guidelines on "Antithrombotic Therapy and Prevention of Thrombosis," states, "For patients initiating VKA

[vitamin K antagonist] therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B)."[125]

- Per the 2008 statement from the American College of Medical genetics (ACMG), "there is insufficient evidence at this time to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naive patients."[126]

Conclusions: Genetic testing may help predict the initial warfarin dose within the first week of warfarin treatment, but the evidence does not support the conclusion that clinically relevant outcomes, such as rates of bleeding or thromboembolism, are improved.

Summary

Antipsychotics Selection and Dosing:

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

Anti-tuberculosis Medications

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

Beta Blocker Selection and Dosing:

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

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

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

Codeine Prescription For Nursing Mothers:

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

Efavirenz Dosing For the Treatment of HIV Infection:

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

H. pylori Infection:

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

Immunosuppressant Dosing For Organ Transplantation:

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

Selective Norepinephrine Reuptake Inhibitors (SNRIs) Selection and Dosing:

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

Selective Serotonin Reuptake Inhibitors (SSRIs) Selection and Dosing:

Individuals with variants in multiple CYP450 genes (eg, CYP2D6 and CYP2C19) have altered metabolism of SSRI drugs. However, the evidence is insufficient to establish how the presence of these

genetic variants affects clinical response to SSRI. Clinical utility for CYP450 (including CYP2D6 and CYP2C19) testing has not been established; it is not known how the genotyping results impact patient management, treatment plans, or health outcomes. Therefore, CYP450 genotyping (including CYP2D6 and CYP2C19) for selection and dosing of SSRIs is considered investigational

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

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

Tricyclic Antidepressants:

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

Warfarin Dosing and Management:

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

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CROSS REFERENCES

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

CODES	NUMBER	DESCRIPTION
CPT	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)
	81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)

	81401	Molecular pathology procedure, Tier 2, Level 2
	81402	Molecular pathology procedure, Tier 2, Level 3
	81404	Molecular pathology procedure, Tier 2, Level 5
	81405	Molecular pathology procedure, Tier 2, Level 6
HCPCS	G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)