

Evidence Based Guideline

Cytochrome p450 Genotyping

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Description of Procedure or Service

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.

Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs. 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.

The cytochrome p450 (CYP450) family is a major subset of all drug-metabolizing enzymes; several CYP450 enzymes are involved in the metabolism of a significant proportion of currently administered drugs. Some CYP450 enzyme genes are highly polymorphic, resulting in some enzyme variants that have variable metabolic capacities among individuals, and some with little to no impact on activity. Thus, CYP450 enzyme variants constitute one important group of drug-gene interactions influencing the variability of effect of some CYP450 metabolized drugs.

Individuals with 2 copies (alleles) of the most common (wild type) DNA sequence of a particular CYP450 enzyme gene resulting in an active molecule are termed extensive metabolizers (EM; normal). Poor metabolizers (PM) lack active enzyme gene alleles, and intermediate metabolizers (IM), who have one active and one inactive enzyme gene allele, may experience to a lesser degree some of the consequences of poor metabolizers. Ultrarapid metabolizers (UM) are individuals with more than 2 alleles of an active enzyme gene. There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme.

Ultrarapid metabolizers administered an active drug may not reach therapeutic concentrations at usual, recommended doses of active drugs, while poor metabolizers may suffer more adverse events at usual doses due to reduced metabolism and increased concentrations. Conversely, for administered prodrugs that must be converted by CYP450 enzymes into active metabolites, ultrarapid metabolizers may suffer adverse effects and poor metabolizers may not respond.

However, it is very important to realize that many drugs are metabolized to varying degrees by more than one enzyme, either within or outside of the CYP450 superfamily. In addition, interaction between different metabolizing genes, interaction of genes and environment, and interactions among different non-genetic factors also influence CYP450-specific metabolizing functions. Thus, identification of a variant in

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a single gene in the metabolic pathway may be insufficient in all but a small proportion of drugs to explain inter-individual differences in metabolism and consequent efficacy or toxicity.

Genetically determined variability in drug response has been traditionally addressed using a trial and error approach to prescribing and dosing, along with therapeutic drug monitoring (TDM) for drugs with a very narrow therapeutic range and/or potential serious adverse effects outside that range. However, TDM is not available for all drugs of interest, and a cautious trial and error approach can lengthen the time to achieving an effective dose.

CYP450 enzyme phenotyping (identifying metabolizer status) can be accomplished by administering a test enzyme substrate to a patient and monitoring parent substrate and metabolite concentrations over time (e.g., in urine). However, testing and interpretation are time-consuming and inconvenient; as a result, phenotyping is seldom performed.

The clinical utility of CYP450 genotyping, i.e., the likelihood that genotyping will significantly improve drug choice/dosing and consequent patient outcomes, is favored when the drug under consideration has a narrow therapeutic dose range (window), when the consequences of treatment failure are severe, and/or when serious adverse reactions are more likely in patients with gene sequence variants. Under these circumstances, genotyping may direct early selection of the most effective drug or dose, and/or avoid drugs or doses likely to cause toxicity. For example, warfarin, some neuroleptics, and tricyclic antidepressants have narrow therapeutic windows and can cause serious adverse events when concentrations exceed certain limits, resulting in cautious dosing protocols. Yet, the potential severity of the disease condition may call for immediate and sufficient therapy; genotyping might speed the process of achieving a therapeutic dose and avoiding significant adverse events.

Diagnostic genotyping tests for certain CYP450 enzymes are now available. Some tests are offered as in-house laboratory-developed test services, which do not require U.S. Food and Drug Administration (FDA) approval but which must meet CLIA quality standards for high complexity testing. The AmpliChip® (Roche Molecular Systems, Inc.) is the only FDA-cleared test for CYP450 genotyping. The AmpliChip® is a microarray consisting of many DNA sequences complementary to 2 CYP450 genes and applied in microscopic quantities at ordered locations on a solid surface (chip). The AmpliChip® tests the DNA from a patient's white blood cells collected in a standard anticoagulated blood sample for 29 polymorphisms and mutations for the CYP2D6 gene and 2 polymorphisms for the CYP2C19 gene. CYP2D6 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 metabolizes several important types of drugs, including proton-pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline. FDA cleared the test "based on results of a study conducted by the manufacturers of hundreds of DNA samples as well as on a broad range of supporting peer-reviewed literature." According to FDA labeling, "Information about CYP2D6 genotype may be used as an aid to clinicians in determining therapeutic strategy and treatment doses for therapeutics that are metabolized by the CYP2D6 product."

Related Policies

Genetic Testing for Warfarin Dosing (CYP2C9)

Genetic Testing for Tamoxifen Treatment (CYP2D6)

*****Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Evidence Based Guideline for Cytochrome p450 Genotyping

CYP450 phenotyping for CYP2C19 *2 and *3 alleles may be appropriate in patients with cardiovascular disease undergoing treatment with clopidogrel (Plavix®) in order to identify those who are poor metabolizers of the drug (patients with CYP2C19*2/2, *3/3, and *2/3 genotypes) and who are, therefore, likely to exhibit poor response to the drug.

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Data on the impact of clopidogrel appears to be particularly strong with multiple studies demonstrating that patients defined as poor metabolizers (CYP2C19 *2/2, *3/3, or *2/3) are at significantly increased risk of a variety of life-threatening adverse cardiovascular events. Because of this strong and significant link between metabolic state and clinical outcomes, the FDA recently issued a public safety communication and re-labeled the drug with a boxed warning about the availability of genetic testing and alternative drug therapies in patients who are found to be poor metabolizers. Alternative treatments, including several that are FDA approved, do exist. Each has its own unique safety and efficacy profile. and none of the alternatives are without their own well-described risks.

Therefore, genotyping for CYP2C19 *2 and *3 alleles may identify poor metabolizers in patients receiving clopidogrel. Treatment alternatives should be carefully selected according to the unique characteristics of each patient found to be a poor metabolizer, and careful follow-up should be performed.

Medical Evidence regarding Cytochrome p450 Genotyping indicates it is not recommended in the following situations

Aside from the use with clopidogrel treatment noted above and the separate policies noted above, genotyping to determine specific cytochrome p450 (CYP450) genetic polymorphisms for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity is not recommended. This includes, but is not limited to, CYP450 genotyping for the following applications:

- selection or dose of selective serotonin reuptake inhibitor (SSRI)
- selection or dose of antipsychotics
- deciding whether to prescribe codeine for nursing mothers
- dose of atomoxetine HCl (approved for treatment of attention-deficit/hyperactivity disorder)
- dose of efavirenz (common component of highly active antiretroviral therapy for HIV infection)
- dose of immunosuppressant for organ transplantation
- selection or dose of beta blockers (e.g., metoprolol)

In general, most published CYP450 pharmacogenomic studies are retrospective evaluations of CYP450 genotype association with intermediate (e.g., circulating drug concentrations) or, less often, final outcomes (e.g., adverse events or efficacy) and are largely small and under-powered to examine the effects of homozygous variant poor metabolizers and of ultrarapid metabolizers, where the strongest effects if any would be seen. There is a lack of prospective evaluation and validation of the clinical utility of CYP450 genotyping to direct therapeutic modifications for improved outcomes.

Benefits Application

This evidence based guideline relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this guideline.

Billing/Coding/Physician Documentation Information

This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: There are no specific CPT or HCPCS codes for this service.

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Scientific Background and Reference Sources

BCBSA 2004 TEC Special Report: Genotyping for Cytochrome P450 Polymorphisms to Determine Drug-Metabolizer Status. Tab 9.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.38, 2/12/09.

Senior Medical Director Review - 4/2009

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.38, 4/8/2010.

Medical Director Review – 3/2011

Policy Implementation/Update Information

- 5/11/09 New Evidence Based Guide adopted from the BCBSA. Reviewed by Senior Medical Director 4/6/2009. "The evidence does not permit conclusions regarding the effect of Cytochrome p450 Genotyping on health outcomes, therefore this test is not recommended." (btw)
- 10/26/09 Specialty Matched Consultant Advisory Panel review meeting 9/28/09. Guideline accepted as written. (adn)
- 6/22/10 Policy Guideline Number(s) removed (amw)
- 4/12/11 Guideline updated. Added Evidence Base Guideline statement; "CYP450 phenotyping for CYP2C19 *2 and *3 alleles may be appropriate in patients with cardiovascular disease undergoing treatment with clopidogrel (Plavix®) in order to identify those who are poor metabolizers of the drug (patients with CYP2C 19*2/2,*3/3, and *2/3 genotypes) and who are, therefore, likely to exhibit poor response to the drug. Data on the impact of clopidogrel appears to be particularly strong with multiple studies demonstrating that patients defined as poor metabolizers (CYP2C19 *2/2, *3/3, or *2/3) are at significantly increased risk of a variety of life-threatening adverse cardiovascular events. Because of this strong and significant link between metabolic state and clinical outcomes, FDA has recently issued a public safety communication and re-labeled the drug with a boxed warning about the availability of genetic testing and alternative drug therapies in patients who are found to be poor metabolizers. Alternative treatments, including several that are FDA approved, do exist although each has its own unique safety and efficacy profile, and none of the alternatives are without their own well-described risks. Therefore, genotyping for CYP2C19 *2 and *3 alleles may be recommended to identify poor metabolizers in patients receiving clopidogrel. Treatment alternatives should be carefully selected according to the unique characteristics of each patient found to be a poor metabolizer and careful follow-up performed." Revised "Benefit Application" section for consistency and clarification. Revised the statement in the "When Not Recommended" section; "Aside from the use with clopidogrel treatment noted above and the separate policies noted above, genotyping to determine specific cytochrome p450 (CYP450) genetic polymorphisms for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity is not recommended. This includes, but is not limited to, CYP450 genotyping for the following applications." Added an additional example of when CYP450 would not be recommended; "selection or dose of beta blockers (e.g., metoprolol)" Reviewed with Medical Director 3/31/2011. Specialty Matched Consultant Advisory Panel review meeting 3/31/11. References added. (btw)

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