Medical Policy
Cytochrome p450 Genotyping

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Policy Number: 256
BCBSA Reference Number: 2.04.38

Related Policies
- Genetic testing for Tamoxifen Treatment, #067
- Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines, #096
- Genetic testing for Warfarin Dose, #214

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members
CYP450 genotyping for the purpose of aiding in the choice of clopidogrel versus alternative anti-platelet agents, or in decisions on the optimal dosing for clopidogrel, may be considered MEDICALLY NECESSARY.

CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for all other drugs is INVESTIGATIONAL, aside from determinations in the separate policies noted above. This includes, but is not limited to, CYP450 genotyping for the following applications:
- Selection or dosing of selective serotonin reuptake inhibitor (SSRI)
- Selection or dosing of antipsychotic drugs
- Deciding whether to prescribe codeine for nursing mothers
- Selection and dosing of selective norepinephrine reuptake inhibitors
- Selection and dosing of tricyclic antidepressants
- Dose of efavirenz (common component of highly active antiretroviral therapy for HIV infection)
- Dosing of immunosuppressant for organ transplantation
- Selection or dose of beta blockers (e.g., metoprolol).

Prior Authorization Information
Commercial Members: Managed Care (HMO and POS)
Prior authorization is **NOT** required.

**Commercial Members: PPO, and Indemnity**
Prior authorization is **NOT** required.

**Medicare Members: HMO Blue℠**
Prior authorization is **NOT** required.

**Medicare Members: PPO Blue℠**
Prior authorization is **NOT** required.

**CPT Codes / HCPCS Codes / ICD-9 Codes**
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

**CPT Codes**

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<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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**Description**

Drug efficacy and toxicity vary substantially across individuals. Various factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited variations or polymorphisms in genes coding for drug metabolizing enzymes may have major effects on the efficacy or toxicity of a drug.

The cytochrome p450 (CYP450) family is a major subset of all drug-metabolizing enzymes and 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 and drug metabolism among individuals, contrasting with some variants having little to no impact on activity.

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 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.

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),
• The consequences of treatment failure are severe, and/or
• 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.

An example of diagnostic genotyping to test for CYP450 enzymes metabolic pathway is the AmpliChip® from Roche Molecular Systems, Inc. All tests for Cytochrome p450 genotyping are considered investigational regardless of the commercial name, the manufacturer or FDA approval status except when used for the medically necessary indications that are consistent with the policy statement.

**Summary**

CYP450 genotyping has been demonstrated in a number of studies to identify increased risk of thrombosis in patients with coronary disease or cardiac interventions being considered as candidates for clopidogrel treatment. This observation is most pronounced for stent thrombosis in patients undergoing PCI. Genotyping may be used to consider treatment alternatives, e.g., higher doses of clopidogrel or alternative drug choices. FDA has created a black box warning indicating testing should be considered. Clinical input from academic medical centers and specialty societies was mixed concerning the benefit of genetic testing, but there was no consensus that the medically necessary determination be changed. As a result, genetic testing for selection and dosing of clopidogrel may be considered medically necessary.

For other medications, 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 underpowered or not designed to examine the clinical effects of homozygous variant poor metabolizers and of ultrarapid metabolizers, where the strongest effects, if any, would be seen. The hazards associated with poor metabolizers are consequently difficult to interpret and decision making about how to use genotyping information is poorly defined with uncertain outcomes. As a result, for most of the indications described above, CYP450 genotyping is investigational.

**Policy History**

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<tbody>
<tr>
<td>1/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>4/2013</td>
<td>BCBSA National medical policy review.</td>
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<tr>
<td></td>
<td>No changes to policy statements.</td>
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<td>No changes to policy statements.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:

- [Medical Policy Terms of Use](#)
- [Managed Care Guidelines](#)
- [Indemnity/PPO Guidelines](#)
- [Clinical Exception Process](#)
- [Medical Technology Assessment Guidelines](#)
References


63. de Leon J. The crucial role of the therapeutic window in understanding the clinical relevance of the poor versus the ultrarapid metabolizer phenotypes in subjects taking drugs metabolized by CYP2D6 or CYP2C19. J Clin Psychopharmacol 2007; 27(3):241-5.


70. Macaluso M, Preskorn SH. CYP 2D6 PM status and antidepressant response to nortriptyline and venlafaxine: is it more than just drug metabolism? J Clin Psychopharmacol 2011; 31(2):143-5.