



Medical Policy Manual

Approved Revision: Do Not Implement Until 12/31/26

Cytochrome p450 Genotyping

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DESCRIPTION

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. CYP2D6 metabolizes approximately 25% of all clinically used medications (e.g., dextromethorphan, beta blockers, antiarrhythmics, antidepressants and morphine derivatives). CYP450 enzyme genes can have distinct variations which can affect individual capability to metabolize specific drugs. CYP450 genotyping has been proposed as a way to direct early selection of the most effective drug or dose to avoid significant adverse events and speed the process of achieving a therapeutic dose.

Diagnostic genotyping tests for certain CYP450 enzymes are available. Several testing kits for CYP450 genotyping have been cleared by FDA. Test kits specific to the CYP2D6 include the AmpliChip® (33 CYP2D6 alleles) and the xTAG® CYP2D6 kit.

Test kits for CYP2C19 include the INFINITI™ CYP2C19 Assay, the Verigene CYP2C19 Nucleic Acid Test, and the Spartan RX® CYP2C19 testing system. Several manufacturers market diagnostic panel tests for genotyping that include multiple CYP450 genes, such as the You Script Panel (CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP3A4, and CYP3A5). Other panel tests include both CYP450 and other non-CYP450 genes involved in drug metabolism, such as the Persona Gene Genetic Panels.

POLICY

- Cytochrome P450 (*CYP2D6*) and (*CYP2C9*) genotyping to determine drug metabolizer status is considered **medically necessary** if the medical appropriateness criteria are met. (See **Medical Appropriateness below**.)
- Cytochrome P450 (*CYP3A5*) genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity(transplants) is considered **medically necessary** if the medical appropriateness criteria are met. (See **Medical Appropriateness below**.)
- Cytochrome P450 (*CYP450*) genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for the following drugs is considered **investigational**:
 - Selection or dosing of clopidogrel
 - Selection or dosing of selective serotonin reuptake inhibitors (SSRIs)
 - Selection or dosing of selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
 - Selection or dosing of tricyclic antidepressants
 - Selection or dosing of antipsychotic drugs
 - Selection or dosing of codeine
 - Selection or dosing of beta blockers
 - Dosing and management of anti-tuberculosis medications
- Cytochrome P450 (*CYP2C19*) genotyping to determine drug metabolizer status in the treatment of *Helicobacter pylori* is considered **investigational**.



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- The use of genetic testing panels that include multiple CYP450 mutations (except for **CYP3A5 as mentioned above**) is considered **investigational**.

MEDICAL APPROPRIATENESS

- Genotyping of Cytochrome P450 (**CYP2D6, CYP2C9, CYP2B6, or CYP3A5**) to determine drug metabolizer status is considered **medically appropriate** if **ANY ONE** of the following are met:
 - CYP2D6** genotyping and **ANY ONE** of the following:
 - Individual with Gaucher disease being considered for treatment with eliglustat
 - Individual with Huntington's disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day
 - Tamoxifen therapy when **ALL** of the following are met:
 - Individual has estrogen receptor-positive breast cancer for which tamoxifen therapy is planned or currently prescribed.
 - Results are expected to influence endocrine treatment selection, dosing, or management.
 - Testing is ordered to identify CYP2D6 metabolizer status prior to or during tamoxifen therapy.
 - CYP2C9** genotyping for relapsing forms of multiple sclerosis (i.e., clinically isolated syndrome, relapsing – remitting disease, active secondary progressive disease) being considered for treatment with siponimod
 - CYP2B6** genotyping for efavirenz-containing HIV therapy when **ALL** of the following are met:
 - Individual has HIV infection.
 - Efavirenz-containing antiretroviral therapy is planned, initiated, or being evaluated because of toxicity concerns.
 - Test results are expected to influence medication selection or dosing.
 - CYP3A5** genotyping for tacrolimus dosing and immunosuppressant for organ transplantation (kidney, heart, lungs, etc) and **ALL** of the following:
 - Organ transplantation is planned or anticipated
 - Tacrolimus therapy is expected
 - Results will be used to guide tacrolimus dosing and immunosuppressive management

IMPORTANT REMINDERS

- Any specific products referenced in this policy are just examples and are intended for illustrative purposes only. It is not intended to be a recommendation of one product over another and is not intended to represent a complete listing of all products available. These examples are contained in the parenthetical e.g. statement.
- We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a member is entitled to receive under his or her health plan, the Member's health plan must be



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reviewed. If there is a conflict between the medical policy and a health plan or government program (e.g., TennCare), the express terms of the health plan or government program will govern.

ADDITIONAL INFORMATION

Individuals with genetic variants of cytochrome P450 have a decreased ability to metabolize clopidogrel, but the impact on clinically meaningful outcomes is uncertain. While genotyping appears in some studies to be helpful in identifying individuals at higher risk of treatment failure and may be useful in selected individuals, more information is needed to refine optimal use of testing and to better understand the relative merit of management options.

CYP3A5 genotype is a clinically relevant predictor of tacrolimus metabolism. Identification of CYP3A5 metabolizer status may assist with individualized tacrolimus dose selection, improve achievement of therapeutic drug concentrations, and support early post-transplant immunosuppressive management. Current transplant literature and CPIC guidance support the clinical utility of genotype-guided tacrolimus dosing in transplant recipients.

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