BlueCross BlueShield of Vermont
An Independent Licensee of the Blue Cross and Blue Shield Association.

Cytochrome P450 Genotype-Guided Treatment Strategy
Corporate Medical Policy

File Name: Cytochrome P450 Genotype-Guided Treatment Strategy
File Code: 2.04.VT38
Origination: 05/2019
Last Review: 01/2025
Next Review: 01/2026
Effective Date: 04/01/2025

Description/Summary

The cytochrome P450 (CYP450) family is involved in the metabolism of many currently administered drugs, and genetic variants in cytochrome P450 are associated with altered metabolism of many drugs. Testing for cytochrome P450 variants may assist in selecting and dosing drugs affected by these genetic variants.

Policy

Coding Information
Click the links below for attachments, coding tables & instructions.
Attachment I – Coding Table

When a service may be considered medically necessary

CYP2D6 genotyping to determine drug metabolizer status may be considered **medically necessary** for individuals:

- With Gaucher disease is being considered for treatment with eliglustat; **OR**
- With Huntington disease is being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day.

CYP2C9 genotyping to determine drug metabolizer status may be considered **medically necessary** for individuals:

- With relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive

disease, being considered for treatment with siponimod.

When a service is considered investigational

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 and indications is considered **investigational**. Investigational uses include, but are not limited to, the following:

- Selection or dosage of codeine
- Dosing of efavirenz and other antiretroviral therapies for HIV infection
- Dosing of immunosuppressants for organ transplantation
- Selection or dosing of ß-blockers (e.g., metoprolol)
- Dosing and management of antitubercular medications
- Dosing and managing warfarin
- Management of treatment with tamoxifen for women at high risk for or with breast cancer
- Dosing and management of medication for treatment of mental health conditions
- Selection of clopidogrel vs. alternative antiplatelet agents, or in decisions regarding the optimal dosing for clopidogrel
- The use of genetic testing panels that include multiple *CYP450* variants

CYP450 genotyping is considered **investigational** for all other indications.

Reference Resources

1. BCBSA Policy 2.04.38 – Cytochrome P450 Genotype-Guided Treatment Strategy. Last Reviewed July 2024. Accessed July 2024.
2. BCBSA Policy 2.04.48 – Genotype-Guided Warfarin Dosing. Last Reviewed July 2024. Accessed July 2024.
3. BCBSA Policy 2.04.110 – Genetic Testing for Diagnosis and Management of Mental Health Conditions. Last Reviewed August 2023. Accessed July 2024.
4. BCBSA Policy 2.04.51 – Genotype-Guided Tamoxifen Treatment. Last Reviewed August 2023. Accessed July 2024.

Document Precedence

Blue Cross and Blue Shield of Vermont (BCBSVT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of

common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language, or employer's benefit plan if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, BCBSVT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract/employer benefit plan language, the member's contract/employer benefit plan language takes precedence.

Audit Information

BCBSVT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, BCBSVT reserves the right to recoup all non-compliant payments.

Administrative and Contractual Guidance

Benefit Determination Guidance

Prior approval is required and benefits are subject to all terms, limitations and conditions of the subscriber contract.

Incomplete authorization requests may result in a delay of decision pending submission of missing information. To be considered compete, see policy guidelines above.

NEHP/ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member's health plan.

Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure. It is important to verify the member's benefits prior to providing the service to determine if benefits are available or if there is a specific exclusion in the member's benefit.

Coverage varies according to the member's group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through an Administrative Services Only (ASO) group, benefits may vary or not apply. To verify benefit information, please refer to the member's employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

Policy Implementation/Update information

05/2019	New Policy. Prior authorization required for codes: 81226, 0028U, 0029U.
09/2021	Policy reviewed. References updated to show BCBSVT Policy reflects use of BCBSA Policies. No change to policy statement. Added code G9143 as investigational. The following codes will require prior approval:81291, 0030U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U. Following codes will change from investigational to requiring prior approval: 81291, 0013U, 0032U, 0033U, 0173U, 0175U.
08/2022	Policy reviewed. References updated. No change to policy statement. Minor grammatical changes.
12/2022	Adaptive Maintenance Cycle Only Effective 01/01/2023: Added code 81418 as investigational to coding table.
10/2023	Policy Reviewed. Addition of *CYP2C9* indication. References updated. Minor formatting changes. Added code 0392U to coding table as investigational to mirror investigational corporate medical policy.
08/2024	Policy reviewed. Minor formatting changes. Consolidated investigational indications under one bulleted section. References updated.
01/2025	Removed code 81291 from coding table from requiring prior approval.

Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).

Approved by BCBSVT Medical Directors

Tom Weigel, MD, MBA
Vice President & Chief Medical Officer

Tammaji P. Kulkarni, MD
Senior Medical Director

Attachment I
Coding Table

Refer to policy instructions for the following codes:		
Code	**Descriptor**	**Instructions**
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)	Requires Prior Approval
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)	Requires Prior Approval
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)	Requires Prior Approval
81230	0 CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)	Requires Prior Approval
81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)	Requires Prior Approval
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)	No Prior Approval Required
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)	Requires Prior Approval
81402	MOLECULAR PATHOLOGY PROCEDURE LEVEL 3(Panels that include the CYP Gene Cytochrome P450 family)	Requires Prior Approval
81404	MOLECULAR PATHOLOGY PROCEDURE LEVEL 5 (Panels that include the CYP Gene Cytochrome P450 family)	Requires Prior Approval
81405	MOLECULAR PATHOLOGY PROCEDURE LEVEL 6(Panels that include the CYP Gene Cytochrome P450 family)	Requires Prior Approval
81418	Drug metabolism genomic sequence panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplications and deletions	Investigational
81479	Unlisted molecular pathology procedure	Requires Prior Approval
0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)	Requires Prior Approval

Refer to policy instructions for the following codes:		
Code	**Descriptor**	**Instructions**
0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)	Requires Prior Approval
0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7)	Requires Prior Approval
0032U	COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant	Requires Prior Approval
0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])	Requires Prior Approval
0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, common and select rare variants (ie, *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)	Requires Prior Approval
0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)	Requires Prior Approval
0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)	Requires Prior Approval
0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)	Requires Prior Approval
0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)	Requires Prior Approval

Refer to policy instructions for the following codes:		
Code	**Descriptor**	**Instructions**
0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)	Requires Prior Approval
0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/multiplication) (List separately in addition to code for primary procedure)	Requires Prior Approval
0156U	Copy number (eg, intellectual disability, dysmorphology), sequence analysis	Requires Prior Approval
0173U	Psychiatry (ie, depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes	Requires Prior Approval
0175U	Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes	Requires Prior Approval
0392U	Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug	Investigational
G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)	Investigational