Clinical Policy: Genetic Testing Pharmacogenetics

Reference Number: CP.MP.232 Coding Implications
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See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Pharmacogenetic tests are germline genetic tests that are developed to aid in assessing an individual's response to a drug treatment or to predict the risk of toxicity from a specific drug treatment. Testing may be performed prior to initiation of treatment to identify if an individual has genetic variants that could either affect response to a particular drug and/or increase the risk of adverse drug reactions. Testing may also be performed during treatment to assess an individual who has had an adverse drug reaction or to assess response to treatment. Test methodology includes genotyping and single nucleotide variant testing.

Below are a list of higher volume tests and the associated laboratories for each criteria section. This list is not all inclusive.

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81225,81226, 81227,81230, 81231,81291, 81355,81381, 81400,81401, 81402,81479	GeneSight Psychotropic Panel, Myriad Genetics	Pharmacogenetic Panel Tests	F01-F69, F80-F99, Z81.8, Z86.59
81225,81226, 81227,81230, 81231,81291, 81355,81381, 81400,81401, 81402,81479	Professional PGX™ (formerly Genecept™ Assay), Genomind	Pharmacogenetic Panel Tests	F01-F69, F80-F99, Z81.8, Z86.59
81225,81226, 81227,81230, 81231,81232, 81240,81241, 81283,81291, 81328,81350, 81355,81381, 81479	Polypharmacy Panel and Polypharmacy Comprehensive Panel, Genelex	Pharmacogenetic Panel Tests	B20, C00.0-C96.9, D00.0-D49.9, E75.22, F01-F99, G10, G71.14, G89.0-G89.4, I20.0, I21.01-I22.9, I24.1, I25.110, I26.01-I26.99, I48.0, I60.00-I66.99, I73, I82.210-I82.91, K50.00-K50.019 K51.00-K51.319, R52, R79.9, T46.6X1A-T46.6X6S, Z13.71-Z13.79, Z80.3, Z81.8,

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
			Z82.49, Z85.3, Z86.000, Z86.59, Z86.71-Z86.79
81225,81226, 81227,81230, 81231,81232, 81240,81241, 81247,81283, 81291,81306, 81328,81335, 81350,81355, 81381,81400, 81401,81402, 81405,81406, 81408,81479	PGxOne™, Admera Health	Pharmacogenetic Panel Tests	B20, C00.0-C96.9, D00.0-D49.9, E75.22, F01-F99, G10, G71.14, G89.0-G89.4, I20.0, I21.01-I22.9, I24.1, I25.110, I26.01-I26.99, I48.0, I60.00-I66.99, I73, I82.210-I82.91, K50.00-K50.019 K51.00-K51.319, R52, R79.9, T46.6X1A-T46.6X6S, Z13.71-Z13.79, Z80.3, Z81.8, Z82.49, Z85.3, Z86.000, Z86.59, Z86.71-Z86.79
81225,81226, 81227,81230, 81231,81232, 81291,81355, 81381,81479	Millennium PGT[SM], Millennium Health (general panel)	Pharmacogenetic Panel Tests	B20, C00.0-C96.9, D00.0-D49.9, E75.22, F01-F99, G10, G71.14, G89.0-G89.4, I20.0, I21.01-I22.9, I24.1, I25.110, I26.01-I26.99, I48.0, I60.00-I66.99, I73, I82.210-I82.91, K50.00-K50.019 K51.00-K51.319, R52, R79.9, T46.6X1A-T46.6X6S, Z13.71-Z13.79, Z80.3, Z81.8, Z82.49, Z85.3, Z86.000, Z86.59, Z86.71-Z86.79
0015U	OneOme RightMed Pharmacogenomic Test, OneOme	Pharmacogenetic Panel Tests	B20, C00.0-C96.9, D00.0-D49.9, E75.22, F01-F99, G10, G71.14, G89.0-G89.4, I20.0, I21.01-

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
			I22.9, I24.1, I25.110, I26.01-I26.99, I48.0, I60.00-I66.99, I73, I82.210-I82.91, K50.00-K50.019 K51.00-K51.319, R52, R79.9, T46.6X1A-T46.6X6S, Z13.71-Z13.79, Z80.3, Z81.8, Z82.49, Z85.3, Z86.000, Z86.59, Z86.71-Z86.79
0029U	Focused Pharmacogenomics Panel, Mayo Medical Laboratories	Pharmacogenetic Panel Tests	I20.0, I21.01-I22.9, I24.1, I25.110, I63.50-I63.549, I66.01-I66.9, I73
0030U	Warfarin Response Genotype, Mayo Medical Laboratories	Pharmacogenetic Panel Tests	I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-Z86.79
0033U	Serotonin Receptor Genotype (HTR2A and HTR2C), Mayo Medical Laboratories	Pharmacogenetic Panel Tests	F01-F69, F80-F99, Z81.8, Z86.59
0078U	INFINITI® Neural Response Panel, PersonalizeDx	Pharmacogenetic Panel Tests	F01-F69, F80-F99, Z81.8, Z86.59
0173U	Psych HealthPGx Panel, RPRD Diagnostics	Pharmacogenetic Panel Tests	F01-F69, F80-F99, Z81.8, Z86.59
0175U	Genomind® Professional PGx ExpressTM CORE, Genomind	Pharmacogenetic Panel Tests	F01-F69, F80-F99, Z81.8, Z86.59
81225,81226, 81227,81230, 81231,81479	Cytochrome P450 panels	Pharmacogenetic Panel Tests	I20.0, I21.01-I22.9, I24.1, I25.110, I63.50-I63.549, I66.01-I66.9, I73
81227,G9143	CYP2C9 Targeted Mutation Analysis	Pharmacogenetic Panel Tests	G35, I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99,

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
			I82.210-I82.91, Z86.71-Z86.79
81225	CYP2C19 Targeted Mutation Analysis	CYP2D6 Variant Analysis	I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-Z86.79
81226,0028U, 0070U,0071U, 0072U,0073U, 0074U,0075U, 0076U	CYP2D6 Targeted Mutation Analysis	CYP2D6 Variant Analysis	C50.011-C50.929, C79.81, D05.00-D05.92, D07.30-D07.39, E75.22, G10, I20.0, I21.01-I22.9, I24.1, I25.110, I63.50-I63.549, I66.01-I66.9, I73, Z13.71-Z13.79, Z80.3, Z85.3, Z86.000
81479, G9143	CYP4F2 Targeted Mutation Analysis	CYP4F2 Variant Analysis	I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-Z86.79
81232	DPYD Targeted Mutation Analysis	DPYD Variant Analysis	C00.0-C96.9, D00.0-D49.9
81381	HLA-B*15:02 Targeted Mutation Analysis	HLA-B*15:02 Variant Analysis	G40
81381, 81374	Carbamazepine Hypersensitivity Pharmacogenomics (Mayo Medical Laboratories)	HLA-B*15:02 and HLA-A*31:01 Variant Analysis	G40
81381	HLA-B*57:01 Targeted Mutation Analysis	HLA-B*57:01 Variant Analysis	B20, Z21
81335	TPMT Targeted Mutation Analysis	TPMT and NUDT15 Variant Analysis	C91.0, K50.00-K50.019 K51.00-K51.319

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81306	NUDT15 Targeted Mutation Analysis	TPMT and NUDT15 Variant Analysis	C91.0, K50.00-K50.019 K51.00-K51.319
0034U	Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping, Mayo Medical Laboratories	TPMT and NUDT15 Variant Analysis	C91.0, K50.00-K50.019 K51.00-K51.319
0169U	NT (NUDT15 and TPMT) genotyping panel, RPRD Diagnostics	TPMT and NUDT15 Variant Analysis	C91.0, K50.00-K50.019 K51.00-K51.319
81350	UGT1A1 Targeted Mutation Analysis	UGT1A1 Variant Analysis	B20, C18, C19, C20, E80.4
81355, G9143	VKORC1 Targeted Mutation Analysis	VKORC1 Variant Analysis	I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-Z86.79
0032U	COMT Targeted Mutation Analysis	Other Single Gene Variant Analysis	F01-F69, F80-F99, G20, Z81.8, Z86.59
0031U	CYP1A2 Targeted Mutation Analysis	Other Single Gene Variant Analysis	F01-F69, F80-F99, Z81.8, Z86.59
81479	KIF6 Targeted Mutation Analysis	Other Single Gene Variant Analysis	E78.0-E78.9, R79.9, Z82.49
81479	OPRM1 Targeted Mutation Analysis	Other Single Gene Variant Analysis	G89.0-G89.4
81328	SLCO1B1 Targeted Mutation Analysis	Other Single Gene Variant Analysis	E78.00-E78.5, G71.14, R79.9, T46.6X1A-T46.6X6S, Z82.49
81346	TYMS Targeted Mutation Analysis	Other Single Gene Variant Analysis	C00.0-C96.9, D00.0-D49.9

This policy document provides criteria for tests that determine the dosage of or the selection of a specific drug based on pharmacogenetic testing. For other related testing, please refer to:

- ***CP.MP.241 Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to DNA testing of a solid tumor or a blood cancer.
- ***CP.MP.224 Genetic Testing: Hematologic Conditions (non-cancerous)*** for criteria related to diagnostic testing for non-cancerous genetic blood disorders.
- ***CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to diagnostic testing for cystic fibrosis, and related therapies.
- ***CP.MP.229 Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for criteria related to *MTHFR* testing.
- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for criteria related to pharmacogenetic testing that are not specifically discussed in this or other specific policies.

Policy/Criteria

Pharmacogenetic Panel Tests

I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of pharmacogenetic testing panels* (81225, 81226, 81227, 81230, 81231, 81232, 81240, 81241, 81247, 81283, 81291, 81306, 81328, 81335, 81350, 81355, 81381, 81400, 81401, 81402, 81405, 81406, 81408, 81479, 0015U, 0029U, 0030U, 0033U, 0078U, 0173U, 0175U, G9143) for all indications.

*See *HLA-B**15:02 and *HLA-A**31:01 Variant Analysis and *TPMT* and *NUDT15* Variant Analysis below for criteria

Pharmacogenetic Single Gene Tests

CYP2C9 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *CYP2C9* variant analysis (81227) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member/enrollee is being considered for treatment with siponimod* (Mayzent®).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *CYP2C9* variant analysis (81227, G9143) for the purpose of managing the administration and dosing of warfarin.

III. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *CYP2C9* variant analysis (81227) to determine drug metabolizer status for all other indications.

*Commonly prescribed for individuals diagnosed with multiple sclerosis

CYP2C19 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *CYP2C19* variant analysis (81225) to determine drug metabolizer status is considered **medically necessary** when meeting either of the following:

   A. The member/enrollee is being considered for treatment with clopidogrel* (Plavix®),

   B. The member/enrollee is currently undergoing treatment with clopidogrel (Plavix®).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *CYP2C19* variant analysis (81225) to determine drug metabolizer status for all other indications.

*Commonly prescribed for acute coronary syndrome and/or following percutaneous coronary intervention

CYP2D6 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *CYP2D6* variant analysis (81226, 0028U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) to determine drug metabolizer status is considered **medically necessary** when meeting any of the following:

   A. The member/enrollee has Gaucher disease and is being considered for treatment with eliglustat (Cerdelga™),

   B. The member/enrollee has Huntington disease and is being considered for treatment with tetrabenazine (Xenazine®) in a dosage greater than 50 mg per day,

   C. The member/enrollee is being considered for treatment with codeine.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *CYP2D6* variant analysis (81226, 0028U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer.

III. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *CYP2D6* variant analysis (81226, 0028U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) to determine drug metabolizer status for all other indications.

CYP4F2 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *CYP4F2* variant analysis (81479, G9143) for the purpose of managing the administration and dosing of warfarin.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *CYP4F2* variant analysis (81479, G9143) to determine drug metabolizer status for all other indications.

DPYD Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *DPYD* variant analysis (81232) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member/enrollee being considered for treatment with any 5-FU containing therapy* (e.g., Fluorouracil®, Xeloda®).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *DPYD* variant analysis (81232) to determine drug metabolizer status for all other indications.

*Commonly prescribed for individuals diagnosed with colorectal, breast, and aerodigestive tract tumors

*HLA-B*15:02* Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *HLA-B*15:02* variant analysis (81381) to determine drug metabolizer status is considered **medically necessary** when meeting either of the following:

   A. The member/enrollee is being considered for treatment with any carbamazepine containing therapy* (e.g., Tegretol®, Carbatrol®),

   B. The member/enrollee is being considered for treatment with phenytoin** (e.g., Dilantin®, Phenytek®).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *HLA-B*15:02* variant analysis (81381) to determine drug metabolizer status for all other indications.

*Commonly prescribed for individuals with epilepsy, trigeminal neuralgia, or bipolar disorder
**Commonly prescribed for treatment of neonatal seizures

*HLA-B*15:02* and *HLA-A*31:01* Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *HLA-B*15:02* and *HLA-B*31:01* variant analysis (81381, 81374) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member/enrollee is being considered for treatment with any carbamazepine containing therapy* (e.g., Tegretol®, Carbatrol®).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *HLA-B*15:02* and *HLA-B*15:02* variant analysis (81381, 81374) to determine drug metabolizer status for all other indications.

*Commonly prescribed for individuals with epilepsy, trigeminal neuralgia, or bipolar disorder

*HLA-B*57:01* Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *HLA-B*57:01* variant analysis (81381) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member/enrollee is being considered for treatment with abacavir* (Ziagen®).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *HLA-B*57:01* variant analysis (81381) to determine drug metabolizer status for all other indications.

*Commonly prescribed for individuals with HIV

*HLA-B*58:01* Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *HLA-B*58:01* variant analysis (81381) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member/enrollee is being considered for treatment with any allopurinol* (e.g. Aloprim® and Zyloprim®) containing therapy.

II. *It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support HLA-B*58:01* variant analysis (81381) to determine drug metabolizer status for all other indications.

*Commonly prescribed for individuals with hyperuricemia, gout, or kidney stones

TPMT and *NUDT15* Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *TMPT* and *NUDT15* variant analysis (81306, 81335, 0034U, 0169U) to determine drug metabolizer status is considered **medically necessary** when meeting either of the following:

   A. The member/enrollee is beginning therapy with azathioprine* (e.g. Imuran and Azasan), mercaptopurine* (e.g. Purinethol® and Purixan®), or thioguanine* (e.g. Tabloid®),

   B. The member/enrollee is on thiopurine therapy and has had abnormal complete blood count results that do not respond to dose reduction.

II. *It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support TPMT* and *NUDT15* variant analysis (81306, 81335, 0034U, 0169U) to determine drug metabolizer status for all other indications.

*Commonly prescribed for patients with autoimmune disorders (e.g. inflammatory bowel disease, Crohn's disease, rheumatoid arthritis) and for treatment of hematologic malignancies (e.g., leukemia and lymphoma)

UGT1A1 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *UGT1A1* variant analysis (81350) to determine drug metabolizer status is considered **medically necessary** when meeting either of the following:

   A. The member/enrollee is beginning irinotecan therapy (e.g., Onivyde®, Camptosar®) for elevated serum bilirubin or Gilbert syndrome,

   B. The member/enrollee is beginning therapy with atazanavir* (e.g. Reyataz®).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support UGT1A1 variant analysis (81350) to determine drug metabolizer status for all other indications.

*Commonly prescribed for patients with HIV

VKORC1 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *VKORC1* variant analysis (81355, G9143) for the purpose of managing the administration and dosing of warfarin.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *VKORC1* variant analysis (81355, G9143) to determine drug metabolizer status for all other indications.

Other Single Gene Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support variant analysis of all other genes for drug metabolizer status, including but not limited to:

   A. *COMT* (0032U)
   B. *CYP1A2* (0031U)
   C. *KIF6* (81479)
   D. *OPRM1* (81479)
   E. *SLCO1B1* (81328)
   F. *TYMS* (81479)

Background

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

The EGAPP Working Group (2007) commissioned the Agency for Healthcare Research and Quality to conduct a systematic review on CYP450 testing in patients receiving SSRIs and 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 complete."

U.S. Food and Drug Administration (FDA):

Pharmacogenetic Testing
On October 31, 2018, the FDA issued a safety communication stating that, "The FDA has become aware of genetic tests with claims to predict how a person will respond to specific medications in cases where the relationship between genetic (DNA) variations and the medication's effects has not been determined. These genetic tests might be offered through health care providers or advertised directly to consumers and claim to provide information on how a patient will respond to medications used to treat conditions such as, depression, heart conditions, acid reflux, and others… The FDA is aware that health care providers may have made inappropriate changes to a patient's medication based on the results from genetic tests that claim to provide information on the personalized dosage or treatment regimens for some antidepressants. Patients and health care providers should not make changes to a patient's medication regimen based on the results from genetic tests that claim to predict a patient's response to specific medications, but are not supported by scientific or clinical evidence to support this use, because doing so may put the patient at risk for potentially serious health consequences. There are a limited number of cases for which at least some evidence does exist to support a correlation between a genetic variant and drug levels within the body, and this is described in the labeling of FDA cleared or approved genetic tests and FDA approved medications."

Siponimod and CYP2C9
The FDA approved siponimod (Mayzent) in March 2019 for the treatment of relapsing forms of multiple sclerosis in adults. This approval was based on a double-blind, randomised, phase 3 study and the CYP2C9 genotype has an impact on the metabolism of siponimod. As part of the FDA approval, CYP2C9 genotype determination should be assessed prior to administration. Dosing regimen is dependent on genotype CYP2C9, specifically *1/*3 or *2/*3 genotype while the presence of CYP2C9*3/*3 is contraindicated.

Clinical Pharmacogenetics Implementation Consortium (CPIC)

Pharmacogenetic testing for mental health disorders
The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2015) conducted a systematic literature review on the influence of CYP2D6 and CYP2C19 genotyping on selective serotonin reuptake inhibitor (SSRI) therapy and provided dosing recommendations for SSRIs based on phenotypes that classified patients as ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. However, CPIC noted that patients on an effective and stable dose of SSRIs would not benefit from dose modifications based on CYP2D6 and CYP2C19 genotype results. Additionally, CPIC asserted that genetic testing is only one factor among several clinical factors that should be considered when determining a therapeutic approach.
The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2016) also conducted a systematic literature review of the influence of CYP2D6 and CYP2C19 genotype on the dosing of tricyclic antidepressants and provided dosing recommendations for tricyclic antidepressants based on patient classifications of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers.

Pharmacogenetic testing for Warfarin dosing
The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2017) updated guidelines for pharmacogenetics-guided warfarin dosing what states that "Although there is substantial evidence associating CYP2C9 and VKORC1 variants with warfarin dosing, randomized clinical trials have demonstrated inconsistent results in terms of clinical outcomes."

CYP2C19 pharmacogenetic testing
The Clinical Pharmacogenetics Implementation Consortium (2013) updated guideline on Clopidogrel dosage based on CYP2C19 genotypes recommends avoiding Clopidogrel for individuals with an intermediate (moderate recommendation) or poor metabolizer (strong recommendation) genotype.
The Clinical Pharmacogenetics Implementation Consortium (2016) updated guideline on Voriconazole dosage based on CYP2C19 genotypes stating that, “Clinical studies have not consistently demonstrated an association between CYP2C19 genotype and adverse reactions. However, as individual patients who are poor metabolizers may have elevated levels leading to toxicity, the use of another antifungal agent is recommended.”

CYP2D6 pharmacogenetic testing
The Clinical Pharmacogenetics Implementation Consortium (CPIC) (2018) published a guideline for tamoxifen prescribing based on CYP2D6 genotype/metabolic phenotype. The guideline acknowledged that there was moderate evidence that CYP2D6 poor metabolizers have a higher risk of breast cancer recurrence or worse event-free survival. However, the evidence was considered weak regarding an association between CYP2D6 metabolizer groups and clinical outcome.
The Clinical Pharmacogenetics Implementation Consortium (CPIC) (2014) published a guideline for codeine therapy based on CYP2D6 genotype/metabolic phenotype. The guideline states that “the association of CYP2D6 metabolizer phenotype with formation of morphine from codeine is well defined” and recommends “using alternative analgesics to codeine in patients who are CYP2D6 poor or ultrarapid metabolizers.

DPYD and TYMS pharmacogenetic testing
The Clinical Pharmacogenetics Implementation Consortium (2017) updated guideline on DYPD and Fluoropyrimidine dosing noted that genetic testing for DPYD may include “resequencing of the complete coding regions” or may be confined to analysis of particular risk variants which may affect 5-fluorouracil toxicity. The guideline further noted that, while other genes (TYMS, MTHFR) may be tested for variants, the clinical utility of such tests is yet unproven. The guideline further stated that in patients who have undergone genetic testing and who are known carriers of a DPYD risk variant, it is recommended to adjust the dosage of 5-fluorouracil-based treatments, or exclude them, depending on the patient’s level of DPYD activity.

*HLA-B*1502 and CYP2C9 pharmacogenetic testing*
The Clinical Pharmacogenetic Implementation Consortium (CPIC) updated the guideline on HLA-B genotyping and carbamazepine dosing (2017) and reaffirmed the original recommendation that “Currently, the Food and Drug Administration recommends that ‘patients with ancestry in at-risk populations should be screened for the presence of HLA-B*15:02 allele

prior to starting carbamazepine'... However, it is important that the prescribing physician bear in mind that many people may be unaware of or fail to disclose more distant Asian ancestry in their families."

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2014) published a guideline on phenytoin prescribing based on HLA-B*1502 and CYP2C9 genotype which recommends against prescribing phenytoin in individuals who are HLA-B*1502 carriers (strong recommendation) and recommends *considering* adjusting starting dose in individuals who are HLA-B*1502 non-carriers who have CYP2C9 poor metabolizer genotype (strong recommendation) or CYP2C9 intermediate metabolizer genotype (moderate recommendation).

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2020) published a therapeutic recommendations for NSAIDs based on CYP2C9 genotype stating that, "The quality of evidence linking genotype to NSAID therapeutic response and adverse events was graded as weak in most cases."

*HLA-B*5701 pharmacogenetic testing*

The Clinical Pharmacogenetic Implementation Consortium (CPIC) updated the guideline on HLA-B genotyping and abacavir dosing (2014) and recommend that "HLA-B*5701 screening should be performed in all abacavir-naive individuals before initiation of abacavir-containing therapy."

*HLA-B*5801 pharmacogenetic testing*

The Clinical Pharmacogenetics Implementation Consortium (2016) revalidated the original recommendation that, "given the high specificity for allopurinol-induced SCAR, allopurinol should not be prescribed to patients who have tested positive for HLA-B*58:01."

SLCO1B1 pharmacogenetic testing

The Clinical Pharmacogenetics and Pharmacogenomics Implementation Consortium (CPIC) (2014) updated guidelines for SLCO1B genotypes and simvastatin-induced myopathy recommended prescribing a lower dose or considering an alternative statin and considering routine creatinine kinase surveillance in patients with SLCO1B genotypes consistent with intermediate or low statin metabolism.

TPMT and NUDT15 pharmacogenetic testing

The Clinical Pharmacogenetic Implementation Consortium (CPIC) (2018) published a guideline on thiopurine dosing based on *TPMT* and *NUDT15* genotypes and recommended that "lower than normal starting doses should be considered in TPMT intermediate metabolizers and markedly reduced doses should be considered in TPMT poor metabolizers to decrease the risk of acute toxicity."

UGT1A1 pharmacogenetic testing

The Clinical Pharmacogenetics and Pharmacogenomics Implementation Consortium (CPIC) (2015) guidelines for *UGT1A1* genotypes and atazanavir prescribing recommended that poor metabolizers consider an alternative agent particularly where jaundice would be of concern to the patient. "A *UGT1A1* genotype is most helpful if available before atazanavir is prescribed" and that "individuals who are homozygous for *UGT1A1*28* or *UGT1A1*6* are very likely to have Gilbert syndrome. Knowing an individual's *UGT1A1* genotype prior to prescribing may have

implications for selection and dosing for drugs known to be *UGT1A1* substrates or inhibitors, such as irinotecan and nilotinib."

COMT and OPRM1 pharmacogenetic testing
The Clinical Pharmacogenetics Implementation Consortium (CPIC) (2021) published a guideline for codeine therapy based on *OPRM1* and *COMT* genotype/metabolic phenotype. The guideline states that "*OPRM1* variants inconsistently have been shown to alter postoperative dose requirements for some opioids. There is evidence for a small increase in postoperative morphine dose requirements (~ 10%) in some clinical studies in patients carrying at least one copy of the

OPRM1 rs1799971 G allele, although the alteration in morphine dose is so modest as to not be clinically actionable. There is also insufficient evidence at this time to conclude altered analgesic response to other opioids in relation to rs1799971, or other *OPRM1* variants. For the most highly studied *COMT* variant, rs4680, there is no evidence to support an association of this variant with opioid adverse events, and there is mixed evidence for an association between *COMT* rs4680 genotype and analgesia or opioid dose requirements. For all other *COMT* variants, there is mixed evidence for an association between *COMT* genotype and analgesia, opioid dose requirements, or adverse events."

National Comprehensive Cancer Network (NCCN)

Pharmacogenetic testing for CYP2D6
Current NCCN breast cancer guidelines (v.2.2021) recommend against *CYP2D6* genotype testing for women being considered for tamoxifen treatment.

Pharmacogenetic testing for 5-Fluorouracil dosing
Current NCCN colon cancer guidelines (v.2.2021) do not recommend use of area under the curve guidance for 5-fluorouracil (5-FU) dosing. NCCN recognizes that pretreatment DPYD testing has the potential to identify the 1-2% of individuals with truncating alleles that may have an increased risk of severe toxicity, but does not currently recommend universal pretreatment genotyping of *DPYD* or *TYMS* variants in patients with colon cancers.

Pharmacogenetic testing for TPMT and *NUDT15*
Current NCCN guidelines on acute lymphoblastic leukemia (v.2.2021) recommend consideration of TPMT gene polymorphisms in patients receiving 6-MP (mercaptopurine), especially in patients who develop severe neutropenia after starting 6-MP. NCCN recommends consideration of TPMT and NUDT15 genotyping for all patients starting 6-MP. Finally they state that quantification of 6-MP metabolites can be very useful in determining whether the lack of myelosuppression is due to non-compliance or hypermetabolism.

American Society of Clinical Oncology (ASCO)
The guidelines from the American Society of Clinical Oncology (2016) on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer stated that "The clinician should not use *CYP2D6* polymorphisms to guide adjuvant endocrine therapy selection and at this point, data do not support the use of *CYP2D6* testing to select patients who may or may not benefit from tamoxifen therapy."

American Academy of Neurology (AAN)
The American Academy of Neurology (2014) published a position paper on the use of opioids for chronic noncancer pain which stated that "genotyping to determine whether the response to opioid therapy can/should be more individualized is an emerging issue that will require critical original research to determine effectiveness and appropriateness of use."

American College of Medical Genetics (ACMG)
The American College of Medical Genetics (2008) policy statement on pharmacogenetic testing concluded: "There is insufficient evidence, at this time, to recommend for or against routine *CYP2C9* and *VKORC1* testing in warfarin-naive patients."

American College of Cardiology Foundation (ACCF) and American Heart Association (AHA)
A consensus statement by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) (2010) on genetic testing for the selection and dosing of clopidogrel states that although clinicians must be aware that genetic variability in CYP enzymes can alter clopidogrel metabolism and that diminished responsiveness to clopidogrel has been associated with adverse patient outcomes the specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined. Furthermore, information regarding the predictive value of pharmacogenomic testing is very limited at this time and the evidence base is insufficient to recommend either routine genetic testing at the present time. The American College of Cardiology Foundation/American Heart Association ACS guidelines (2012) noted that genetic testing for *CYP2C19* loss-of-function alleles may be considered on a case-by-case basis, especially for patients who experience recurrent ACS events despite ongoing therapy with clopidogrel. In addition, the committee recommended that genotyping might be considered if results of testing may alter management, which they suggest until better clinical evidence exists to provide a more scientifically derived recommendation.

Coding Implications
This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2021, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	02/22	02/22

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

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Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.