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CONCERT GENETIC TESTING: TOXICOLOGY AND PHARMACOGENETICS (VERSION B)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

OVERVIEW

This policy addresses the use of tests for drug and treatment response and toxicity testing. Test specifications/technology and sample type vary widely depending on the substance(s) of interest and the clinical question being asked.

For additional information see the [Rationale](#) section.

POLICY REFERENCE TABLE

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 2024, 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.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage. Please see the [Concert Platform](#) for additional registered tests.

CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Pharmacogenetic Panel Tests			
Pharmacogenetic Panel Tests Validated Tests	GeneSight (Assurex Health) 0345U	81418, 0029U, 0033U, 0173U, 0175U, 0286U, 0345U, 0347U, 0348U, 0349U, 0350U, 0392U, 0411U, 0419U, 0423U, 0434U, 0438U, 0460U, 0461U, 0476U, 0477U, 0516U, 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-	1, 2, 3, 4, 5, 6, 32
	Neuropharmagen (Precision Molecular Solutions) 81418		
	PGXPSYCH (PHD Laboratory LLC): 81418		
	Psychotropic Pharmacogenomics Gene Panel (Mayo): 81418		
	Focused Pharm Panel (Mayo): 0029U		
IDgenetix (Castle): 0411U			

	Tempus nP (Tempus): 0419U	T46.6X6S, Z13.71-Z13.79, Z80.3, Z81.8, Z82.49, Z85.3, Z86.000, Z86.59, Z86.71-Z86.79	
Mental Health Panel (Exceltox Laboratories LLC): 81418	PGX (PHD Laboratory LLC): 81418		
PGS SHORT COMP (PHD Laboratory LLC): 81418	Sinochips PGx Comprehensive (Sinochips Kansas LLC): 81418		
Carolina Comprehensive PGx (Carolina Diagnostics Lab): 81418	COR120 - Comprehensive Pharmacogenetic Test (Quantigen LLC): 81418		
PCL PGX+ Comprehensive Report (Patients Choice Laboratories of Indiana, LLC): 81418)	PharmGx Comprehensive PGx Panel (Dxome Clia Laboratory, Inc): 81418		

	PsychPainMakers Panel (Genemarkers): 81418		
	PredictScript Poly (Phenomics Health Inc): 81418		
	PredictScriptCNS (Phenomics Health Inc): 81418		
Pharmacogenetic Single Gene Tests			
<u>BCHE Variant Analysis</u>	BCHE Single Gene Test (Blueprint Genetics)	81479, Z01.81, Z01.810, Z01.811, Z01.818, Z01.89	8
<u>CYP2C9 Variant Analysis</u>	Cytochrome P450 2C9 Genotype (Quest Diagnostics)	81227, E78.00, E78.1, G35, I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210- I82.9, Z86.71-Z86.79	8
<u>CYP2C19 Variant Analysis</u>	AccuType CP, Clopidogrel CYP2C19 Genotype (Quest Diagnostics)	81225, C64, F32, I21.0-I22.9, I24.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.9, K21.9, L20, Q85.83, R56.9, R68.82, Z86.71-Z86.79	8
<u>CYP2D6 Variant Analysis</u>	CYP2D6 (ARUP Laboratories)	81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U, C50.011- C50.92, C79.81, D05.00- D05.92, D07.30-D07.39,	7, 8
	CYP2D6 Common Variants and Copy Number - 0070U (Mayo Clinic Laboratories)		

	CYP2D6 Full Gene Sequencing - 0071U (Mayo Clinic Laboratories)	E11.9, E75.22, F11, F20.9, F31, F33, F84.0, F90, F95.2, G10, G24, G47.419, I10, I20.0, I21.01-I22.9, I24.1, I25.110, I48, I63.50-I63.549, I66.01- I66.9, I73, K21.9, R42, R52, T75.3, Z13.71-Z13.79, Z80.3, Z85.3, Z86.000	
	CYP2D6-2D7 Hybrid Gene Targeted Sequence Analysis - 0072U (Mayo Clinic Laboratories)		
	CYP2D7-2D6 Hybrid Gene Targeted Sequence Analysis - 0073U (Mayo Clinic Laboratories)		
	CYP2D6 Nonduplicated Gene Analysis - 0074U (Mayo Clinic Laboratories)		
	CYP2D6 5' gene duplication/multiplication targeted sequence analysis - 0075U (Mayo Clinic Laboratories)		
	CYP2D6 3' gene duplication/multiplication targeted sequence analysis - 0076U (Mayo Clinic Laboratories)		
CYP3A5 Variant Analysis	Pain Management, CYP450 3A5 Genotype, Qualitative (Quest Diagnostics)	81231, T86, Z79.6, Z94	8
CYP4F2 Variant Analysis	CYP4F2 Single Gene Test (Blueprint Genetics)	81479, I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-	8

		Z86.79	
<u>DPYD Variant Analysis</u>	DPYD Genotyping (Labcorp)	81232, C69, C69.4	8
<u>HLA-A*02:01 Variant Analysis</u>	HLA A 02:01 Determination (Quest Diagnostics)	81379, 81380, 81381, C69, C69.4	11, 12
	HLA-A*02:01-Specific (LabCorp)		
	HLA-A*02:01 Determination (Versiti)		
<u>HLA-B*15:02 Variant Analysis</u>	HLA-B*15:02, Carbamazepine Sensitivity (Labcorp)	81381, G40	8
<u>HLA-B*57:01 Variant Analysis</u>	HLA B*57:01 Abacavir Hypersensitivity (Labcorp)	81381, B20, Z21	8
<u>NAT2 Variant Analysis</u>	NAT2 single gene test (Blueprint Genetics)	81479, G73, M35.9	8
<u>TPMT and NUDT15 Variant Analysis</u>	Thiopurine S-Methyltransferase (TPMT) Genotype (Quest Diagnostics)	81306, 81335, 0034U, 0169U, C91.0, K50.00-K50.90, K51.00-K51.319, M35.9, M05-M06.9, C85.90	8, 10
	TPMT and NUDT15 (ARUP Laboratories)		
	Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping - 0034U (Mayo Clinic Laboratories)		

	NT (NUDT15 and TPMT) genotyping panel - 0169U (RPRD Diagnostics)		
UGT1A1 Variant Analysis	UGT1A1 Irinotecan Toxicity (Labcorp)	81350, B20, C18, C19, C20, C50, C84, E80.4	8
UGT2B17 Variant Analysis	UGT2B17 Single Gene (Fulgent Genetics)	81479, C25, C64, C71, C72, Q85.83	8
VKORC1 Variant Analysis	VKORC1 Targeted Variant - Single Test (GeneDx)	81355, I21.0-I22.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, Z86.71-Z86.79	8
Warfarin Sensitivity Panel Tests			
Warfarin Sensitivity Analysis Panels	Warfarin Response Genotype - 0030U (Mayo Medical Laboratories)	81227, 81355, 0030U, I21, I26, I48	8, 9
	Accutype Warfarin (Quest)		
Other Pharmacogenetic Single Gene Variant Tests			
Other Pharmacogenetic Single Gene Variant Analysis	Catechol-O-Methyltransferase (COMT) Genotype - 0032U (Mayo Clinic Laboratories)	81479, 0031U, 0032U	8
	Cytochrome P450 1A2 Genotype - 0031U (Mayo Clinic Laboratories)		

	Cardio IQ KIF6 Genotype (Quest Diagnostics)		
	Opioid Receptor, mu OPRM1 Genotype, 1 Variant (ARUP Laboratories)		
	TYMS Single Gene (Sequencing & Deletion/Duplication) (Fulgent Genetics)		

RELATED POLICIES

This policy document provides criteria for testing related to toxicology and pharmacogenetics. Please refer to:

- **Oncology Testing: Solid Tumor Molecular Diagnostics** for criteria related to molecular profiling of a known or suspected cancer (e.g. broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).
- **Specialty Testing: Hematology** for criteria related to diagnostic tests for benign (non-cancerous) hematologic conditions including sickle cell disease, inherited anemias, and hemophilias.
- **Specialty Testing: Respiratory** for criteria related to diagnostic testing for cystic fibrosis and related therapies.
- **Specialty Testing: Nutrition and Metabolism** for criteria related to diagnostic and serum biomarker tests for nutritional status and biochemical disorders.
- **General Approach to Laboratory Testing** or criteria related to toxicology and pharmacology that is not specifically discussed in this or another non-general policy.

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CRITERIA

It is the policy of health plans affiliated with Centene Corporation[®] that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

PHARMACOGENETIC PANEL TESTS

Pharmacogenetic Panel Tests

- I. Pharmacogenetic panel tests are considered **medically necessary** when:
 - A. The member is age 18 years or older, **AND**
 - B. The member is being considered for, or is already being treated with, one or more specific medication(s) related to their diagnosis that is known to have a gene-drug interaction, **AND**
 - C. The pharmacogenetic panel test requested is one of the following (has proven clinical validity, as demonstrated through independent evaluation from a recognized third-party source, including but not limited to MolDx, ECRI, Hayes, Optum Genomics or FDA):
 1. GeneSight (Assurex Health): 0345U
 2. Neuropharmagen (Precision Molecular Solutions) 81418
 3. PGXPSYCH (PHD Laboratory LLC): 81418
 4. Psychotropic Pharmacogenomics Gene Panel (Mayo): 81418
 5. Focused Pharm Panel (Mayo): 0029U
 6. IDgenetix (Castle): 0411U
 7. Tempus nP (Tempus): 0419U
 8. Mental Health Panel (Exceltox Laboratories LLC): 81418
 9. PGX (PHD Laboratory LLC): 81418

10. PGS SHORT COMP (PHD Laboratory LLC): 81418
11. Sinochips PGx Comprehensive (Sinochips Kansas LLC): 81418
12. Carolina Comprehensive PGx (Carolina Diagnostics Lab): 81418
13. COR120 - Comprehensive Pharmacogenetic Test (Quantigen LLC):
81418
14. PCL PGX+ Comprehensive Report (Patients Choice Laboratories of
Indiana, LLC): 81418
15. PharmGx Comprehensive PGx Panel (Dxome Clia Laboratory, Inc):
81418
16. PsychPainMakers Panel (Genemarkers): 81418
17. PredictScript Poly (Phenomix Health Inc): 81418
18. PredictScriptCNS (Phenomix Health Inc): 81418 **AND**

- D. The member has a diagnosis of any of the following for which treatment is being considered:
1. Major depressive disorder, **OR**
 2. Generalized anxiety disorder.
- II. Current evidence does not support pharmacogenetic panel tests for all other indications, including:
- A. As an initial screening test for medication selection.

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PHARMACOGENETIC SINGLE GENE TESTS

BCHE Variant Analysis

- I. *BCHE* variant analysis to determine drug metabolizer status is considered **medically necessary** when:

- A. The member/enrollee is being considered for or is currently undergoing treatment with either of the following:
 - 1. Mivacurium¹ (e.g., Mivacron), **OR**
 - 2. Succinylcholine¹ (e.g., Anectine, Suxamethonium).
- II. Current evidence does not support *BCHE* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly used as a muscle relaxant during surgery or intubation.

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***CYP2C9* Variant Analysis**

- I. *CYP2C9* variant analysis to determine drug metabolizer status is considered **medically necessary** when:
 - A. The member/enrollee is being considered for or is currently undergoing treatment with any of the following:
 - 1. Siponimod¹ (e.g., Mayzent), **OR**
 - 2. Celecoxib² (e.g., Celebrex, Elyxyb), **OR**
 - 3. Dronabinol³ (e.g., Marinol, Syndros), **OR**
 - 4. Erdafitinib⁴ (e.g., Balversa), **OR**
 - 5. Flurbiprofen⁵ (e.g., Ansaid), **OR**
 - 6. Fosphenytoin⁶ (e.g., Cerebyx, Sesquient), **OR**
 - 7. Meloxicam⁷ (e.g., Anjeso, Mobic, Vivlodex, Qmiiz ODT), **OR**
 - 8. Nateglinide⁸ (e.g., Starlix), **OR**

9. Phenytoin⁹ (e.g., Dilantin, Phenytek), **OR**

10. Piroxicam¹⁰ (e.g., Feldene), **OR**

11. Warfarin¹¹ (e.g., Coumadin, Jantoven).

II. Current evidence does not support *CYP2C9* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed for individuals diagnosed with multiple sclerosis

² Commonly prescribed for treating pain or inflammation

³ Commonly prescribed for treating loss of appetite and severe nausea and vomiting

⁴ Commonly prescribed for treatment of bladder cancer

⁵ Commonly prescribed for treatment of pain or inflammation

⁶ Commonly prescribed for preventing or controlling seizures

⁷ Commonly prescribed for treating pain, inflammation, or severe pain

⁸ Commonly prescribed for blood sugar control in individuals with type II diabetes

⁹ Commonly prescribed for treatment of seizures

¹⁰ Commonly prescribed to treat pain or inflammation

¹¹ Commonly prescribed to reduce the formation of blood clots

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***CYP2C19* Variant Analysis**

I. *CYP2C19* variant analysis to determine drug metabolizer status is considered **medically necessary** when:

A. The member/enrollee is being considered for or is currently undergoing treatment with any of the following:

1. Clopidogrel¹ (e.g., Plavix), **OR**
2. Abrocitinib² (e.g., Cibinqo), **OR**
3. Belzutifan³ (e.g., Welireg), **OR**
4. Brivaracetam⁴ (e.g., Briviact, Brivajoy), **OR**
5. Citalopram⁵ (e.g., Celexa), **OR**
6. Clobazam⁶ (e.g., Onfi), **OR**
7. Flibanserin⁷ (e.g., Addyi), **OR**
8. Pantoprazole⁸ (e.g., Protonix).

II. Current evidence does not support *CYP2C19* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed after an angina or cardiac arrest to lower risk of stroke and blood clots

² Commonly prescribed for eczema

³ Commonly prescribed to treat tumors in individuals with Von Hippel-Lindau syndrome

⁴ Commonly prescribed to treat seizures

⁵ Commonly prescribed for treatment of depression and major depressive disorder

⁶ Commonly prescribed for treatment of seizures caused by Lennox-Gastaut syndrome

⁷ Commonly prescribed for low libido in pre-menopausal women

⁸ Commonly prescribed for treatment of erosive esophagitis caused by GERD, and Zollinger-Ellison syndrome

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***CYP2D6* Variant Analysis**

- I. *CYP2D6* variant analysis to determine drug metabolizer status is considered **medically necessary** when:
 - A. The member/enrollee is being considered for or is currently undergoing treatment with any of the following:
 1. Eliglustat¹ (e.g., Cerdelga), **OR**
 2. Tetrabenazine² (e.g., Xenazine), **OR**
 3. Amphetamine³ (e.g., Adzenys, Dyanavel, Evekeo), **OR**
 4. Aripiprazole⁴ (e.g., Abilify, Abilify Maintena), **OR**
 5. Aripiprazole lauroxil⁵ (e.g., Aristada), **OR**
 6. Atomoxetine⁶ (e.g., Strattera), **OR**
 7. Brexpiprazole⁷ (e.g., Rexulti), **OR**
 8. Clozapine⁸ (e.g., Versacloz, FazaClo, Clozaril), **OR**
 9. Deutetrabenazine⁹ (e.g., Austedo), **OR**
 10. Gefitinib¹⁰ (e.g., Iressa), **OR**
 11. Iloperidone¹¹ (e.g., Fanapt), **OR**
 12. Lofexidine¹² (e.g., Lucemyra), **OR**
 13. Meclizine¹³ (e.g., Antivert, Bonine, Dramamine, Verticalm, Zentrip), **OR**
 14. Metoclopramide¹⁴ (e.g., Reglan, Metozolv), **OR**
 15. Oliceridine¹⁵ (e.g., Olinvyk), **OR**

16. Pimozide¹⁶ (e.g., Orap), **OR**
17. Pitolisant¹⁷ (e.g., Wakix), **OR**
18. Propafenone¹⁸ (e.g., Rythmol), **OR**
19. Thioridazine¹⁹ (e.g., Mellaril), **OR**
20. Tramadol²⁰ (e.g., ConZip, Ultram), **OR**
21. Valbenazine²¹ (e.g., Ingrezza), **OR**
22. Venlafaxine²² (e.g., Effexor), **OR**
23. Vortioxetine²³ (e.g., Trintellix, Brintellix), **OR**
24. Codeine²⁴.

II. Current evidence does not support *CYP2D6* variant analysis to determine drug metabolizer status for all other indications, including:

- A. For the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer.

¹ Commonly prescribed for treatment of Gaucher disease

² Commonly prescribed for treatment of involuntary movements (chorea) caused by Huntington disease

³ Commonly prescribed for treatment of hyperactivity, impulse control, and attention deficit hyperactivity disorder (ADHD)

⁴ Commonly prescribed for schizophrenia, bipolar I disorder, and major depressive disorder

⁵ Commonly prescribed for schizophrenia

⁶ Commonly prescribed for treatment of attention deficit hyperactivity disorder (ADHD)

⁷ Commonly prescribed for treatment of schizophrenia and major depressive disorder

⁸ Commonly prescribed for treatment of schizophrenia

- ⁹ Commonly prescribed for treatment of involuntary muscle movements (chorea) caused by Huntington disease, and tardive dyskinesia
- ¹⁰ Commonly prescribed for treatment of non-small cell lung cancer
- ¹¹ Commonly prescribed for treatment of schizophrenia
- ¹² Commonly prescribed for treatment of opioid withdrawal symptoms
- ¹³ Commonly prescribed for treatment of motion sickness and vertigo
- ¹⁴ Commonly prescribed for treatment of heartburn caused by GERD, gastroparesis, nausea and vomiting, and to aid in certain medical procedures involving the stomach or intestines
- ¹⁵ Commonly prescribed for treatment of severe pain
- ¹⁶ Commonly prescribed for treatment of Tourette's syndrome
- ¹⁷ Commonly prescribed for treatment of excessive daytime sleepiness or sudden loss of muscle strength (cataplexy) related to narcolepsy
- ¹⁸ Commonly prescribed for treatment of heart rhythm disorders
- ¹⁹ Commonly prescribed for treatment of schizophrenia
- ²⁰ Commonly prescribed for treatment of moderate to severe pain
- ²¹ Commonly prescribed for treatment of tardive dyskinesia
- ²² Commonly prescribed for treatment of major depressive disorder, anxiety, and panic disorder
- ²³ Commonly prescribed for treatment of major depressive disorder
- ²⁴ Commonly prescribed for treatment of mild to moderately severe pain, and to help reduce coughing

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***CYP3A5* Variant Analysis**

- I. *CYP3A5* variant analysis to determine drug metabolizer status is considered **medically necessary** when:
 - A. The member/enrollee is being considered for or is currently undergoing treatment with tacrolimus¹ (e.g., Protopic, Envarsus, Astagraf, Prograf).
- II. Current evidence does not support *CYP3A5* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed to individuals who have undergone a heart, kidney, liver, or lung transplant

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***CYP4F2* Variant Analysis**

- I. *CYP4F2* variant analysis to determine drug metabolizer status is considered **medically necessary** when:
 - A. The member/enrollee is being considered for or is currently undergoing treatment with warfarin¹ (e.g., Coumadin, Jantoven).
- II. Current evidence does not support *CYP4F2* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed to reduce the formation of blood clots

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***DPYD* Variant Analysis**

- I. *DPYD* variant analysis to determine drug metabolizer status is considered **medically necessary** when:

- A. The member/enrollee is being considered for or is currently undergoing treatment with either of the following:
 - 1. Fluorouracil¹ (e.g., Carac, Efudex, Tolak, Fluoroplex), **OR**
 - 2. Capecitabine¹ (e.g., Xeloda).
- II. Current evidence does not support *DPYD* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed for individuals diagnosed with colorectal, breast, and aerodigestive tract tumors

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***HLA-A*02:01* Variant Analysis**

- I. *HLA-A*02:01* variant analysis is considered **medically necessary** when the member/enrollee meets the following:
 - A. The member/enrollee is age 18 or older, **AND**
 - B. The member/enrollee has a diagnosis of one of the following:
 - 1. Metastatic uveal melanoma, **OR**
 - 2. Unresectable uveal melanoma.
- II. Current evidence does not support *HLA-A*02:01* variant analysis for all other indications.

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***HLA-B*15:02* Variant Analysis**

- I. *HLA-B*15:02* variant analysis to determine drug metabolizer status is considered **medically necessary** when:

- A. The member/enrollee is being considered for or is currently undergoing treatment with any of the following:
1. Carbamazepine containing therapy¹ (e.g., Tegretol, Carbatrol, Epitol, Equetro), **OR**
 2. Phenytoin² (e.g., Dilantin, Phenytek), **OR**
 3. Fosphenytoin² (e.g., Cerebyx, Sesquient).
- II. Current evidence does not support *HLA-B*15:02* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed for individuals with epilepsy, trigeminal neuralgia, or bipolar disorder

² Commonly prescribed for treatment of seizures

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***HLA-B*57:01* Variant Analysis**

- I. *HLA-B*57:01* variant analysis to determine drug metabolizer status is considered **medically necessary** when:
- A. The member/enrollee is being considered for or is currently undergoing treatment with abacavir¹ (e.g., Ziagen).
- II. Current evidence does not support *HLA-B*57:01* variant analysis to determine drug metabolizer for all other indications.

¹ Commonly prescribed for individuals with HIV

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***NAT2* Variant Analysis**

- I. *NAT2* variant analysis to determine drug metabolizer status is considered **medically necessary** when:
 - A. The member/enrollee is being considered for or is currently undergoing treatment with amifampridine/amifampridine phosphate¹ (e.g., Firdapse, Ruzurgi).
- II. Current evidence does not support *NAT2* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed for treatment of Lambert-Eaton myasthenic syndrome

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***TPMT* and *NUDT15* Variant Analysis**

- I. *TPMT* and *NUDT15* variant analysis to determine drug metabolizer status is considered **medically necessary** when:
 - A. The member/enrollee is being considered for or is currently undergoing treatment with any of the following:
 1. Azathioprine¹ (e.g., Imuran and Azasan), **OR**
 2. Mercaptopurine² (e.g., Purinethol and Purixan), **OR**
 3. Thioguanine³ (e.g., Tabloid), **OR**
 - B. The member/enrollee is on thiopurine therapy, **AND**
 1. The member/enrollee has had abnormal complete blood count results.
- II. Current evidence does not support *TPMT* and *NUDT15* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed for treatment of avoiding rejection of a transplanted organ, and rheumatoid arthritis

² Commonly prescribed for treatment of acute lymphoblastic or lymphocytic leukemia

³ Commonly prescribed for treatment of acute nonlymphocytic leukemia

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***UGT1A1* Variant Analysis**

I. *UGT1A1* variant analysis to determine drug metabolizer status is considered **medically necessary** when:

A. The member/enrollee is being considered for or is currently undergoing treatment with any of the following:

1. Irinotecan¹ (e.g., Onivyde, Camptosar), **OR**
2. Belinostat² (e.g., Beleodaq), **OR**
3. Sacituzumab govitecan-hziy³ (e.g., Trodelvy).

II. Current evidence does not support *UGT1A1* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed for treatment of colon, rectal and pancreatic cancers

² Commonly prescribed for treatment of peripheral T-cell lymphoma

³ Commonly prescribed for treatment of breast and urothelial cancers

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***UGT2B17* Variant Analysis**

- I. *UGT2B17* variant analysis to determine drug metabolizer status is **medically necessary** when:
 - A. The member/enrollee is being considered for or is currently undergoing treatment with belzutifan¹ (e.g., Welireg).
- II. Current evidence does not support *UGT2B17* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed to treat tumors in individuals with Von Hippel-Lindau syndrome

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***VKORC1* Variant Analysis**

- I. *VKORC1* variant analysis to determine drug metabolizer status is considered **medically necessary** when:
 - A. The member/enrollee is being considered for or is currently undergoing treatment with warfarin¹ (e.g., Coumadin, Jantoven).
- II. Current evidence does not support *VKORC1* variant analysis to determine drug metabolizer status for all other indications.

¹ Commonly prescribed to reduce the formation of blood clots

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WARFARIN SENSITIVITY PANEL TESTS

Warfarin Sensitivity Analysis Panels

- I. Multigene panel analysis to determine drug metabolizer status for warfarin¹ sensitivity is considered **medically necessary** when:
 - A. The member/enrollee is being considered for or is undergoing treatment with warfarin, **AND**
 1. The member/enrollee has not reached a therapeutic dose, **AND**
 - B. The member/enrollee is undergoing prophylaxis and treatment of venous thrombosis or pulmonary embolism, **OR**
 - C. The member/enrollee is undergoing prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, **OR**
 - D. The member/enrollee has a history of previous myocardial infarction.
- II. Current evidence does not support multigene panel analysis to confirm drug metabolizer status for warfarin¹ sensitivity for all other indications.

¹ Commonly prescribed to reduce the formation of blood clots

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OTHER PHARMACOGENETIC SINGLE GENE VARIANT TESTS

Other Pharmacogenetic Single Gene Variant Analysis

- I. Current evidence does not support variant analysis of all other genes for drug metabolizer status, including but not limited to:
 - A. *COMT* (0032U, 81479)
 - B. *CYP1A2* (0031U, 81479)
 - C. *KIF6* (81479)
 - D. *OPRM1* (81479)
 - E. *TYMS* (81479).

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BACKGROUND AND RATIONALE

Pharmacogenetic Panel Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled “MoIDX: Pharmacogenomics Testing” states the following: “PGx tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in

the patient’s condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable...”

Bunka et al

In their 2023 rapid review and meta-analysis, Bunka et al discuss the age of patients who have participated in studies related to the use of pharmacogenetic panels. The authors note that there is currently insufficient evidence to support ordering PGx tests for adolescents as a part of their treatment for depression (p. 5).

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***BCHE* Variant Analysis**

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations, which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, lists the following recommendations for *BCHE*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Mivacurium	BCHE	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (prolonged neuromuscular blockade). Avoid use in poor metabolizers.
Succinylcholine	BCHE	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (prolonged neuromuscular blockade). Avoid use in poor metabolizers. May administer a test dose to assess sensitivity and administer cautiously via slow infusion.

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CYP2C9 Variant Analysis

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, list the following recommendations for *CYP2C9*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Celecoxib	CYP2C9	poor metabolizers or *3 carriers	Results in higher systemic concentrations. Reduce starting dose to half of the lowest recommended dose in poor metabolizers. Consider alternative therapy in poor metabolizers with juvenile rheumatoid arthritis.
Dronabinol	CYP2C9	intermediate or poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Erdafitinib	CYP2C9	*3/*3 (poor metabolizers)	May result in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Flurbiprofen	CYP2C9	poor metabolizers or *3 carriers	Results in higher systemic concentrations. Use a reduced dosage in poor metabolizers.
Fosphenytoin	CYP2C9	intermediate or poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk (central nervous system toxicity). Consider starting at the lower end of the dosage range and monitor serum concentrations. Refer to FDA labeling for specific dosing recommendations. Carriers of CYP2C9*3 alleles may be at increased risk of severe cutaneous adverse reactions. Consider avoiding fosphenytoin as an alternative to carbamazepine in patients who

			are CYP2C9*3 carriers. Genotyping is not a substitute for clinical vigilance and patient management.
Meloxicam	CYP2C9	poor metabolizers or *3 carriers	Results in higher systemic concentrations. Consider dose reductions in poor metabolizers. Monitor patients for adverse reactions.
Nateglinide	CYP2C9	poor metabolizers	Results in higher systemic concentrations and may result in higher adverse reaction risk (hypoglycemia). Dosage reduction is recommended. Increase monitoring frequency for adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Phenytoin	CYP2C9	intermediate or poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk (central nervous system toxicity). Refer to FDA labeling for specific dosing recommendations. Carriers of CYP2C9*3 alleles may be at increased risk of severe cutaneous adverse reactions. Consider avoiding phenytoin as an alternative to carbamazepine in patients who are CYP2C9*3 carriers. Genotyping is not a substitute for clinical vigilance and patient management.
Piroxicam	CYP2C9	intermediate or poor metabolizers	Results in higher systemic concentrations. Consider reducing dosage in poor metabolizers.
Siponimod	CYP2C9	intermediate or poor metabolizers	Results in higher systemic concentrations. Adjust dosage based on genotype. Do not use in patients with CYP2C9 *3/*3 genotype. Refer to FDA labeling for specific dosing recommendations.
Warfarin	CYP2C9	intermediate or poor metabolizers	Alters systemic concentrations and dosage requirements. Select initial dosage, taking into

			account clinical and genetic factors. Monitor and adjust dosages based on INR.
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CYP2C19 Variant Analysis

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, list the following recommendations for *CYP2C19*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Abrocitinib	CYP2C19	poor metabolizers	Results in higher systemic concentrations and may result in higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Belzutifan	CYP2C19 and/or UGT2B17	poor metabolizers	Results in higher systemic concentrations and may result in higher adverse reaction risk (anemia, hypoxia). Monitor patients who are poor metabolizers for both genes for adverse reactions.
Brivaracetam	CYP2C19	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Consider dosage reductions in poor metabolizers.
Citalopram	CYP2C19	poor metabolizers	Results in higher systemic concentrations and adverse reaction risk (QT prolongation). The maximum recommended dose is 20 mg.
Clobazam	CYP2C19	intermediate or poor metabolizers	Results in higher systemic active metabolite concentrations. Poor metabolism results in higher adverse

			reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Clopidogrel	CYP2C19	intermediate or poor metabolizers	Results in lower systemic active metabolite concentrations, lower antiplatelet response, and may result in higher cardiovascular risk. Consider use of another platelet P2Y12 inhibitor.
Flibanserin	CYP2C19	poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk. Monitor patients for adverse reactions.
Pantoprazole	CYP2C19	intermediate or poor metabolizers	Results in higher systemic concentrations. Consider dosage reduction in children who are poor metabolizers. No dosage adjustment is needed for adult patients who are intermediate or poor metabolizers.

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***CYP2D6* Variant Analysis**

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (6.2024) recommend against *CYP2D6* genotype testing for women being considered for tamoxifen treatment (p. DCIS-2 and p. BINV-K 2 of 2).

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, list the following recommendations for *CYP2D6*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Amphetamine	CYP2D6	poor metabolizers	May affect systemic concentrations and adverse reaction risk. Consider a lower starting dosage or use an alternative agent.
Aripiprazole	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Aripiprazole Lauroxil	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Atomoxetine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Adjust titration interval and increase dosage if tolerated. Refer to FDA labeling for specific dosing recommendations.
Brexpiprazole	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Clozapine	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Dosage reductions may be necessary.

Codeine	CYP2D6	ultrarapid metabolizers	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (life-threatening respiratory depression and death). Codeine is contraindicated in children under 12 years of age.
Deutetrabenazine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and adverse reaction risk (QT prolongation). The maximum recommended dosage should not exceed 36 mg (maximum single dose of 18 mg).
Eliglustat	CYP2D6	ultrarapid, normal, intermediate, or poor metabolizers	Alters systemic concentrations, effectiveness, and adverse reaction risk (QT prolongation). Indicated for normal, intermediate, and poor metabolizer patients. Ultrarapid metabolizers may not achieve adequate concentrations to achieve a therapeutic effect. The recommended dosages are based on CYP2D6 metabolizer status. Coadministration with strong CYP3A inhibitors is contraindicated in intermediate and poor CYP2D6 metabolizers. Refer to FDA labeling for specific dosing recommendations.

Gefitinib	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Iloperidone	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation). Reduce dosage by 50%.
Lofexidine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Monitor for orthostatic hypotension and bradycardia.
Meclizine	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May affect systemic concentrations. Monitor for adverse reactions and clinical effect.
Metoclopramide	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. The recommended dosage is lower. Refer to FDA labeling for specific dosing recommendations.
Oliceridine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (respiratory depression and sedation). May require less frequent dosing.

Pimozide	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Dosages should not exceed 0.05 mg/kg in children or 4 mg/day in adults who are poor metabolizers and dosages should not be increased earlier than 14 days.
Pitolisant	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Use the lowest recommended starting dosage. Refer to FDA labeling for specific dosing recommendations.
Propafenone	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (arrhythmia). Avoid use in poor metabolizers taking a CYP3A4 inhibitor.
Tetrabenazine	CYP2D6	poor metabolizers	Results in higher systemic concentrations. The maximum recommended single dose is 25 mg and should not exceed 50 mg/day.
Thioridazine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation). Predicted effect based on experience with CYP2D6 inhibitors. Contraindicated in poor metabolizers.

Tramadol	CYP2D6	Ultrarapid metabolizers	Results in higher systemic and breast milk active metabolite concentrations, which may result in respiratory depression and death. Contraindicated in children under 12 and in adolescents following tonsillectomy/adenoidectomy. Breastfeeding is not recommended during treatment.
Valbenazine	CYP2D6	poor metabolizers	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (QT prolongation). Dosage reductions may be necessary.
Venlafaxine	CYP2D6	poor metabolizers	Alters systemic parent drug and metabolite concentrations. Consider dosage reductions.
Vortioxetine	CYP2D6	poor metabolizers	Results in higher systemic concentrations. The maximum recommended dose is 10 mg.

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***CYP3A5* Variant Analysis**

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, lists the following recommendations for *CYP3A5*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Tacrolimus	CYP3A5	intermediate or normal metabolizers	Results in lower systemic concentrations, lower probability of achieving target concentrations and may result in higher rejection risk. Measure drug concentrations and adjust dosage based on trough whole blood tacrolimus concentrations.

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***CYP4F2* Variant Analysis**

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, list the following recommendations for *CYP4F2*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Warfarin	CYP4F2	V433M variant carriers	May affect dosage requirements. Monitor and adjust doses based on INR.

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***DPYD* Variant Analysis**

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, list the following recommendations for *DPYD*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Capecitabine	DPYD	intermediate or poor metabolizers	Results in higher adverse reaction risk (severe, life-threatening, or fatal toxicities). No dosage has proven safe in poor metabolizers, and insufficient data are available to recommend a dosage in intermediate metabolizers. Withhold or discontinue in the presence of early-onset or unusually severe toxicity.
Fluorouracil	DPYD	intermediate or poor metabolizer	Results in higher adverse reaction risk (severe, life-threatening, or fatal toxicities). No dosage has proven safe in poor metabolizers and insufficient data are available to recommend a dosage in intermediate metabolizers. Withhold or discontinue in the presence of early-onset or unusually severe toxicity.

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HLA-A*02:01 Variant Analysis

Food and Drug Administration (FDA):

“KIMMTRAK [(tebentafusp-tebn)] is a bispecific gp100 peptide-HLA-directed CD3 T cell engager indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma” (p. 1).

Chen, et al.

“Tebentafusp...should be the preferred frontline agent for most HLA-A*0201 positive patients. However, patients with rapidly progressing disease or high tumor benefit may not derive the same benefit” (p. 1).

“In most cases, tebentafusp should be the preferred front-line agent for the treatment of metastatic uveal melanoma. However, it is limited to patients with HLA-A2*0201 positivity and

may not be the preferred upfront agent in patients with rapidly progressing disease or high tumor burden” (p. 17).

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HLA-B*15:02 Variant Analysis

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, list the following recommendations for *HLA-B*15:02*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Carbamazepine	HLA-B	*15:02 allele positive	Results in higher adverse reaction risk (severe skin reactions). Avoid use unless potential benefits outweigh risks and consider risks of alternative therapies. Patients positive for HLA-B*15:02 may be at increased risk of severe skin reactions with other drugs that are associated with a risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Genotyping is not a substitute for clinical vigilance.
Fosphenytoin	HLA-B	*15:02 allele positive	May result in higher adverse reaction risk (severe cutaneous reactions). Patients positive for HLA-B*15:02 may be at increased risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Consider avoiding fosphenytoin as an alternative to carbamazepine in patients who are positive for HLA-B*15:02. Genotyping is not a substitute for clinical vigilance and patient management.
Phenytoin	HLA-B	*15:02 allele positive	May result in higher adverse reaction risk (severe cutaneous reactions). Patients positive for HLA-B*15:02 may be at increased risk of Stevens Johnson

			Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Consider avoiding phenytoin as an alternative to carbamazepine in patients who are positive for HLA-B*15:02. Genotyping is not a substitute for clinical vigilance and patient management.
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HLA-B*57:01 Variant Analysis

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, list the following recommendations for *HLA-B*57:01*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Abacavir	HLA-B	*57:01 allele positive	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for HLA-B*57:01.

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NAT2 Variant Analysis

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations, which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, lists the following recommendations for *NAT2*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
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Amifampridine	NAT2	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Use lowest recommended starting dosage and monitor for adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Amifampridine Phosphate	NAT2	poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions.

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TPMT and NUDT15 Variant Analysis

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, list the following recommendations for *TPMT* and *NUDT15*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Azathioprine	TPMT and/or NUDT15	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Consider alternative therapy in poor metabolizers. Dosage reduction is recommended in intermediate metabolizers for NUDT15 or TPMT. Intermediate metabolizers for both genes may require more substantial dosage

			reductions. Refer to FDA labeling for specific dosing recommendations.
Mercaptopurine	TPMT and/or NUDT15	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Initial dosages should be reduced in poor metabolizers; poor metabolizers generally tolerate 10% or less of the recommended dosage. Intermediate metabolizers may require dosage reductions based on tolerability. Intermediate metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.
Thioguanine	TPMT and/or NUDT15	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Initial dosages should be reduced in poor metabolizers; poor metabolizers generally tolerate 10% or less of the recommended dosage. Intermediate metabolizers may require dosage reductions based on tolerability. Intermediate

			metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.
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National Comprehensive Cancer Network (NCCN)

The NCCN guideline for acute lymphoblastic leukemia (3.2024) recommends that, for patients receiving treatment with 6-MP, testing for *TPMT* gene polymorphisms is recommended for patients who develop severe myelosuppression after starting 6-MP (ALL-D, MS-15, MS-29, MS-50, MS-51, MS-53).

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UGT1A1 Variant Analysis

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, list the following recommendations for *UGT1A1*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Belinostat	UGT1A1	*28/*28 (poor metabolizers)	May result in higher systemic concentrations and higher adverse reaction risk. Reduce starting dose to 750 mg/m2 in poor metabolizers.
Irinotecan	UGT1A1	*1/*6, *1/*28 (intermediate metabolizers) or *6/*6, *6/*28, *28/*28 (poor metabolizers)	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (severe or life-threatening neutropenia, severe diarrhea). Closely monitor for neutropenia during and after treatment. Consider reducing the starting dosage by at

			least one level in poor metabolizers and modify the dosage based on individual patient tolerance. Refer to FDA labeling for specific dosing recommendations.
Sacituzumab Govitecan-hziy	UGT1A1	*28/*28 (poor metabolizers)	May result in higher systemic concentrations and adverse reaction risk (neutropenia). Monitor for adverse reactions and tolerance to treatment.

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UGT2B17 Variant Analysis

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations, which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, lists the following recommendations for *UGT2B17*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Belzutifan	CYP2C19 and/or UGT2B17	poor metabolizers	Results in higher systemic concentrations and may result in higher adverse reaction risk (anemia, hypoxia). Monitor patients who are poor metabolizers for both genes for adverse reactions.

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VKORC1 Variant Analysis

Food and Drug Administration (FDA)

The FDA published a Table of Pharmacogenetic Associations which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, list the following recommendations for *VKORC1*:

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Warfarin	VKORC1	-1639G>A variant carriers	Alters dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.

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Warfarin Sensitivity Analysis Panels

Food and Drug Administration (FDA)

Per the FDA label, the indications and usage for Warfarin include the following:

- Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism
- Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement
- Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction

The FDA published a Table of Pharmacogenetic Associations, which details possible gene-drug interactions. Section 1, entitled Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations, lists the following recommendations for *CYP2C9*, *CYP4F2* and *VKORC1*:

Warfarin	CYP2C9	intermediate or poor metabolizers	Alters systemic concentrations and dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.
	CYP4F2	V433M variant carriers	May affect dosage requirements. Monitor and adjust doses based on INR.

	VKORC1	-1639G>A variant carriers	Alters dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.
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Other Pharmacogenetic Single Gene Variant Analysis

The Food and Drug Administration (FDA) does not list *COMT*, *CYP1A2*, *KIF6*, *OPRM1*, or *TYMS* in Section 1 of the Table of Pharmacogenetic Associations (“Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations”).

DEFINITIONS

1. **Clinical validity**, according to the National Institutes of Health-Department of Energy (NIH-DOE) Task Force on Genetic Testing, describes the accuracy with which a test identifies a particular clinical condition. The components of measuring clinical validity are:
 - a. **Sensitivity**: among people with a specific condition, the proportion who have a positive test result
 - b. **Specificity**: among people who do not have the condition, the proportion who have a negative test result
 - c. **Positive predictive value**: among people with a positive test result, the proportion of people who have the condition
 - d. **Negative predictive value**: among people with a negative test result, the proportion who do not have the condition

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
<p>Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced “coverage criteria” with “criteria. For Policy Reference Table; under Pharmacogenetic Single Gene Tests: added “BCHE Variant Analysis and related content; under CYP2C9 Variant Analysis: added “E78.00, E78.1”; under CYP2C19 Variant Analysis: added “C64, F32”; added “K21.9, L20, Q85.83, R56.9, R68.82”; under CYP2D6 Variant Analysis: added “C50.11-C50.929...”; added CYP3A5 Variant Analysis and related content; added NAT2 Variant Analysis and related content; for UGT1A1 Variant Analysis: added “C50, C84”. For Other Related Policies: added “and Molecular”. For Criteria: added BCHE Variant Analysis and related content; under CYP2C9 Variant Analysis: I.A. added “or is currently undergoing”, added “Siponimod...”; I.B.-I.K. added “The member/enrollee is being considered...”; under II.A. removed “For the purpose of managing...”; added “Commonly prescribed for treating...”; under CYP2C19 Variant Analysis: under I.C.-I.I. “The member/enrollee is being considered...”; added “Commonly prescribed for treating...”; under CYP2D6 Variant Analysis: under I.A. removed “has Gaucher disease”; added “or is currently undergoing”; under I.B. added “or is currently...”; under I.C. added “The member/enrollee is being considered...”; removed “codeine”; added “amphetamine...”; under I.D.-I.X. added “The member/enrollee is being considered...”; added 1-24 “Commonly prescribed for...”; for DPYD Variant Analysis: under I.A. added “or is currently undergoing”; removed “any 5-FU containing...”; added “Fluorouacil”; added “Andrucil...”; added I.B. “The member/enrollee is being considered...”; for HLA-B*15:02 Variant Analysis: under I.A. added “or is currently undergoing”; added “Epitol, Equetro”; under I.B. added “or is currently undergoing”; removed “I. HLA-B*15:02...”; for HLA-B*57:01 Variant Analysis: under I.A. added “or is currently undergoing”; for NAT2 Variant Analysis: under I. and II. replaced “HLA-B*58.01” with “NAT2”; replaced “81381” with “81479”; under I.A. added “or is currently undergoing”; removed “allopurinol”; added “amifampridine...”; removed “Aloprim...”; added “Firdapse...”; for TPMT and NUDT15 Variant Analysis: under A. removed “beginning therapy”; added “being considered for...”; removed “mercaptopurine”; added I.B.and I.C. “The member/enrollee is being considered...”; removed “patients with autoimmune...”; added “treatment of avoiding...”; added 2, 3 “Commonly prescribed...”; for UGT1A1 Variant Analysis: under I.A. removed “beginning irinotecan therapy”; added “being considered...”; under I.C. added “The member/enrollee is being considered...”; under</p>	10/23	10/23

Reviews, Revisions, and Approvals	Revision Date	Approval Date
<p>I. Replaced “patients with” with “patients with HIV”; added 2-3 “Commonly prescribed...”; added UGT2B17 Variant Analysis,,, for VKORC1 Variant Analysis: under I. removed “for the purpose...”; added “to determine drug metabolizer status”; removed “investigational”; added “medically necessary when:...”; removed “A. For the purpose...”; added “1. Commonly prescribed...”. For Other Single Gene Variant Analysis: under I.F. removed “81346”. For Background and Rationale: removed “a given patient...”; added “A rapid review...”; removed “where the Clinical Pharmacogenetics...”; added “BCHE Variant Analysis...”; for CYP2C9 Variant Analysis: removed “The FDA approved...”; added “The FDA published a Table...”; removed “The Clinical Pharmacogenetics...”; for CYP2C19 Variant Analysis: removed “Clinical Pharmacogenetics...”; added “The FDA published...”; for CYP2D6 Variant Analysis: removed “Clinical Pharmacogenetics...”; removed “American Society...”; removed “CYP4F2 Variant Analysis...”; added “Food and Drug Administration...”; added “CYP3A5 Variant Analysis...”; added “CYP4F2 Variant Analysis...”; for DPYD Variant Analysis: removed “Clinical Pharmacogenetics...”; added “The FDA published...”; for HLA-B*15:02 Variant Analysis: removed :Clinical Pharmacogenetics...”; added “Food and Drug Administration...”; for NAT2 Variant Analysis: removed :Clinical Pharmacogenetics...”; added “Food and Drug Administration...”; for TPMT and NUDT15 Variant Analysis: removed “National Comprehensive Cancer Network...”; added “Food and Drug...”; for UGT1A1 Variant Analysis: removed :Clinical Pharmacogenetics...”; removed “Other Single Gene Variant Analysis...”; added “Food and Drug...”; for UGT2B17 Variant Analysis: added “Food and Drug...”; for VKORC1 Variant Analysis: added “Food and Drug...”; for Other Single Gene Variant Analysis: added “The Food and Drug...”</p>		
<p>Added CPT codes 0423U, 0434U, 0437U, 0438U to the policy coding reference table and criteria for Pharmacogenetic Panel Tests.member/enrollee is being considered...”; removed “codeine”; added “amphetamine...”; under I.D.-I.X. added “The member/enrollee is being considered...”; added 1-24 “Commonly prescribed for...”; for DPYD Variant Analysis: under I.A. added “or is currently undergoing”; removed “any 5-FU containing...”; added “Fluorouacil”; added “Andrucil...”; added I.B. “The member/enrollee is being considered...”; for HLA-B*15:02 Variant Analysis: under I.A. added “or is currently undergoing”; added “Epitol, Equetro”; under I.B. added “or is currently undergoing”; removed “I. HLA-B*15:02...”; for HLA-B*57:01 Variant Analysis: under I.A. added “or is currently undergoing”; for NAT2 Variant Analysis: under I. and II. replaced “HLA-B*58.01” with “NAT2”; replaced “81381” with “81479”; under I.A. added “or is currently undergoing”; removed “allopurinol”; added</p>	11/23	

Reviews, Revisions, and Approvals	Revision Date	Approval Date
<p>“amifampridine...”; removed “Aloprim...”; added “Firdapse...”; for TPMT and NUDT15 Variant Analysis: under A. removed “beginning therapy”; added “being considered for...”; removed “mercaptapurine”; added I.B.and I.C. “The member/enrollee is being considered...”; removed “patients with autoimmune...”; added “treatment of avoiding...”; added 2, 3 “Commonly prescribed...”; for UGT1A1 Variant Analysis: under I.A. removed “beginning irinotecan therapy”; added “being considered...”; under I.C. added “The member/enrollee is being considered...”; under I. Replaced “patients with” with “patients with HIV”; added 2-3 “Commonly prescribed...”; added UGT2B17 Variant Analysis,,, for VKORC1 Variant Analysis: under I. removed “for the purpose...”; added “to determine drug metabolizer status”; removed “investigational”; added “medically necessary when:...”; removed “A. For the purpose...”; added “1. Commonly prescribed...”. For Other Single Gene Variant Analysis: under I.F. removed “81346”. For Background and Rationale: removed “a given patient...”; added “A rapid review...”; removed “where the Clinical Pharmacogenetics...”; added “BCHE Variant Analysis...”; for CYP2C9 Variant Analysis: removed “The FDA approved...”; added “The FDA published a Table...”; removed “The Clinical Pharmacogenetics...”; for CYP2C19 Variant Analysis: removed “Clinical Pharmacogenetics...”; added “The FDA published...”; for CYP2D6 Variant Analysis: removed “Clinical Pharmacogenetics...”; removed “American Society...”; removed “CYP4F2 Variant Analysis...”; added “Food and Drug Administration...”; added “CYP3A5 Variant Analysis...”; added “CYP4F2 Variant Analysis...”; for DPYD Variant Analysis: removed “Clinical Pharmacogenetics...”; added “The FDA published...”; for HLA-B*15:02 Variant Analysis: removed :Clinical Pharmacogenetics...”; added “Food and Drug Administration...”; for NAT2 Variant Analysis: removed :Clinical Pharmacogenetics...”; added “Food and Drug Administration...”; for TPMT and NUDT15 Variant Analysis: removed “National Comprehensive Cancer Network...”; added “Food and Drug...”; for UGT1A1 Variant Analysis: removed :Clinical Pharmacogenetics...”; removed “Other Single Gene Variant Analysis...”; added “Food and Drug...”; for UGT2B17 Variant Analysis: added “Food and Drug...”; for VKORC1 Variant Analysis: added “Food and Drug...”; for Other Single Gene Variant Analysis: added “The Food and Drug...”</p>		
<p>Semi-annual review. Updated title to reflect V2.2024 version. In Warfarin Sensitivity Analysis Panels, clinical criteria section added to allow coverage of small targeted panels for this indication. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.</p>	04/24	04/24

Reviews, Revisions, and Approvals	Revision Date	Approval Date
<p>Semi-annual review. Modified Concert Genetic Testing: Pharmacogenetics V2.2024 to create new policy: Concert Genetic Testing: Pharmacogenetics (Version B). Pharmacogenetic Panel Testing: Replaced previous criteria that stated pharmacogenetic panels were not medically necessary with criteria based on LCD guidelines for medical necessity for generalized anxiety disorder and major depressive disorder indications when meeting additional criteria; added further support in the Background and Rationale section with an additional reference (Bunka et al), specifically justifying the age of 18 years or older within coverage criteria; updated Policy Reference Table accordingly. Other Pharmacogenetic Single Gene Variant Analysis: Removed SLCO1B1 from list of non-covered genes to be consistent with LCD guidelines; Added "Pharmacogenetic" to name of criteria; Removed SLOC1B1 test from Policy Reference Table and criteria. CYP3A5 Variant Analysis: Updated example test in Policy Reference Table. UGT1A1 Variant Analysis: Updated footnote for commonly prescribed indications. VKORC1 Variant Analysis: Added drug brand names in criteria. DPYD Variant Analysis: Added drug brand names in criteria.</p> <p>CYP2D6 Variant Analysis: Fixed clerical error in Policy Reference Table; Added drug brand name in criteria; Updated NCCN version in Background and Rationale and references. Warfarin Sensitivity Analysis Panels: Reformatted criteria for ease of use. CYP2C19 Variant Analysis: Removed criteria needed for coverage to be consistent with FDA guidelines; Updated test in Policy Reference Table. TPMT and NUDT15 Variant Analysis: Reformatted criteria for ease of use, added NCCN guideline to Background and Rationale and references. HLA A 02:01 Variant Analysis: New criteria set created.</p>	10/24	10/24
<p>Annual review. Pharmacogenetic panel test criteria: Specified that pharmacogenetic panel tests must have proven clinical validity, as demonstrated through independent evaluation from a recognized third-party source including but not limited to MolDX, ECRI, Hayes, Optum Genomics or FDA, and removed redundant language; added the following to the list of medically necessary tests: Focused Pharm Panel, Tempus nP, Mental Health Panel, PGX, PGS SHORT COMP, Sinochips PGx Comprehensive, Carolina Comprehensive PGx, COR 120 – Comprehensive Pharmacogenetic Test, PCL PGX+ Comprehensive Report, PharmGx Comprehensive PGx Panel, PsychPainMakers Panel, PredictScript Pol, PredictScriptCNS. CYP2C19 Variant Analysis criteria: Corrected typo from Cobazam to Clobazam. HLA-A*02:01 Variant Analysis criteria: Removed criterion I.B.3 requiring that the member not have rapid progression of disease. TPMT and NUDT15 Variant Analysis criteria: Removed language in criterion B1 requiring evidence of non-response to dose-reduction to better align with existing guidelines; A spelling error was corrected in the TPMT</p>	11/25	12/25

Reviews, Revisions, and Approvals	Revision Date	Approval Date
gene. “Investigational” policy statements replaced with “current evidence does not support...” Updated table of commonly billed codes, rationale and references.		

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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.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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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 and 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.

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