Medica Central Coverage Policy

Policy Name:	**Genetic Testing: Pharmacogenetics MP9602**
Effective Date:	**January 01, 2025**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica Central plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.

Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number. https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

Medica Central coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

OVERVIEW

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 gene sequencing, deletion/duplication analysis, and single nucleotide variant testing.

POLICY REFERENCE TABLE

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage.

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Pharmacogenetic Panel Tests	GeneSight Psychotropic (Myriad Genetics)	0345U	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	1, 2, 3, 4, 5, 6
	Professional PGX (formerly Genecept Assay) (Genomind)	81418		
	PGxOne (Admera Health)			
	Genomind Professional PGX Express CORE	0175U		
	Cytochrome P450 Genotyping Panel (ARUP Laboratories)	81418		
	OneOme RightMed Pharmacogenomic Test (OneOme, LLC)	0347U		
	RightMed Comprehensive Test Exclude F2 and F5 (OneOme, LLC)	0348U		
	RightMed Comprehensive Test (OneOme, LLC)	0349U		
	RightMed Gene Report (OneOme, LLC)	0350U		
	RightMed Oncology Gene Report (OneOme, LLC)	0460U		
	RightMed Oncology Medication Report (OneOme, LLC)	0461U		
	Focused Pharmacogenomics Panel (Mayo Clinic Laboratories)	0029U		
	Psych HealthPGx Panel, (RPRD Diagnostics)	0173U		

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
	CNT Genotyping Panel (RPRD Diagnostics)	0286U		
	PersonalisedRX (Lab Genomics LLC)	0380U		
	Serotonin Receptor Genotype (HTR2A and HTR2C), (Mayo Medical Laboratories)	0033U		
	EffectiveRX Comprehensive Panel (GENETWORx)	0438U		
	RightMed Gene Test Exclude F2 and F5 (OneOme LLC)	0434U		
	Genomind Pharmacogenetics Report (Genomind, Inc)	0423U		
	Tempus nP (Tempus)	0419U		
	IDgenetix (Castle Biosciences)	0411U		
	Medication Management Neuropsychiatric Panel (RCA Laboratory)	0392U		
	RightMed Mental Health Gene Report (OneOme, LLC)	0476U		
	RightMed Mental Health Medication Report (OneOme, LLC)	0477U		
	MyGenVar Pharmacogenomics Test (Geisinger Medical Laboratories)	0516U		
Pharmacogenetic Single Gene Tests				
BCHE Variant Analysis	BCHE Single Gene Test (Blueprint	81479	Z01.81, Z01.810, Z01.811, Z01.818, Z01.89	8

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
	Genetics)			
CYP2C9 Variant Analysis	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-I82.91, Z86.71-Z86.79	8
CYP2C19 Variant Analysis	CYP2C19 Single Gene Test (Blueprint Genetics)	81225, 81479	C64, F32, I21.0-I22.9, I24.9, I26.01-I26.99, I48.0, I60.00-I66.99, I82.210-I82.91, K21.9, L20, Q85.83, R56.9, R68.82, Z86.71-Z86.79	8
CYP2D6 Variant Analysis	CYP2D6 (ARUP Laboratories)	81226	C50.011-C50.929, C79.81, D05.00-D05.92, D07.30-D07.39, 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	7, 8
	CYP2D6 Common Variants and Copy Number (Mayo Clinic Laboratories)	0070U		
	CYP2D6 Full Gene Sequencing (Mayo Clinic Laboratories)	0071U		
	CYP2D6-2D7 Hybrid Gene Targeted Sequence Analysis (Mayo Clinic Laboratories)	0072U		
	CYP2D7-2D6 Hybrid Gene Targeted Sequence Analysis (Mayo Clinic Laboratories)	0073U		
	CYP2D6 Nonduplicated Gene Analysis (Mayo Clinic Laboratories)	0074U		
	CYP2D6 5' gene duplication/multiplication targeted sequence	0075U		

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
	analysis (Mayo Clinic Laboratories)			
	CYP2D6 3' gene duplication/multiplication targeted sequence analysis (Mayo Clinic Laboratories)	0076U		
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-Z86.79	8
DPYD Variant Analysis	DPYD Genotyping (Labcorp)	81232	C00.0-C96.9, D00.0-D49.9	8
*HLA-A**02:01 Variant Analysis	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)			
*HLA-B**15:02 Variant Analysis	HLA-B*15:02, Carbamazepine Sensitivity (Labcorp)	81381	G40	8
*HLA-B**57:01 Variant Analysis	HLA B*57:01 Abacavir Hypersensitivity (Labcorp)	81381	B20, Z21	8
NAT2 Variant Analysis	NAT2 single gene test (Blueprint Genetics)	81479	G73, M35.9	8
TPMT and *NUDT15* Variant Analysis	Thiopurine S-Methyltransferase (*TPMT*) Genotype (Quest Diagnostics)	81335	C91.0, K50.00-K50.90 K51.00-K51.319, M35.9, M05-M06.9, C85.90	8, 10

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
	TPMT and *NUDT15* (ARUP Laboratories)	81335, 81306		
	Thiopurine Methyltransferase (*TPMT*) and Nudix Hydrolase (*NUDT15*) Genotyping (Mayo Clinic Laboratories)	0034U		
	NT (*NUDT15* and *TPMT*) genotyping panel (RPRD Diagnostics)	0169U		
UGT1A1 Variant Analysis	*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 Single Gene Test (Blueprint Genetics)	81355, 81479	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 Analysis Panels	Warfarin Response Genotype (Mayo Medical Laboratories)	0030U	I21, I26, I48	8, 9
	Accutype Warfarin (Quest)	81227, 81355		
Other Pharmacogenetic Single Gene Variant Analysis	Catechol-O-Methyltransferase (COMT) Genotype (Mayo Clinic Laboratories)	0032U	F01-F69, F80-F99, G20, Z81.8, Z86.59	8
	COMT single gene test (Blueprint Genetics)	81479		
	Cytochrome P450 1A2 Genotype (Mayo Clinic Laboratories)	0031U	F01-F69, F80-F99, Z81.8, Z86.59	

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
	CYP1A2 single gene test (Blueprint Genetics)	81479		
	Cardio IQ KIF6 Genotype (Quest Diagnostics)	81479	E78.0-E78.9, R79.9, Z82.49	
	Opioid Receptor, mu OPRM1 Genotype, 1 Variant (ARUP Laboratories)	81479	G89.0-G89.4	
	TYMS Single Gene (Sequencing & Deletion/Duplication) (Fulgent Genetics)	81479	C00.0-C96.9, D00.0-D49.9	

OTHER RELATED POLICIES

This policy document provides coverage 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:

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

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COVERAGE CRITERIA

Pharmacogenetic Panel Tests

I. Pharmacogenetic panel tests (0029U, 0175U, 0345U, 0380U, 0411U, 0419U, 81418, 81479)[1] 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 being considered has proven clinical validity, **AND**

D. The pharmacogenetic panel test being considered has proven clinical utility, **AND**

E. The member has a diagnosis of any of the following for which a treatment medication is being considered:

1. Major depressive disorder, **OR**

2. Generalized anxiety disorder.

II. Pharmacogenetic panel tests (0029U, 0175U, 0345U, 0380U, 0411U, 0419U, 81418, 81479) are considered **investigational** for all other indications, including:

A. As an initial screening test for medication selection.

[1]Example Tests and CPT codes: GeneSight (Assurex Health): 0345U; Genomind Professional PGx Express (Genomind): 0175U; NeuroIDgenetix (AltheaDx): 81479; Neuropharmagen (Precision Molecular Solutions) 81418; PGXPSYCH (PHD Laboratory LLC) 81418; Psychotropic Pharmacogenomics Gene Panel (Mayo): 81418; Focused Pharm Panel (Mayo): 0029U; Personalised RX (Lab Genomics, Agena Biosciences): 0380U; IDgenetix (Castle): 0411U; Tempus nP (Tempus): 0419U

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PHARMACOGENETIC SINGLE GENE TESTS

BCHE Variant Analysis

I. *BCHE* variant analysis (81479) to determine drug metabolizer status is considered **medically necessary** when:

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

1. Mivacurium[1] (e.g., Mivacron), **OR**

2. Succinylcholine[1] (e.g., Anectine, Suxamethonium).

II. *BCHE* variant analysis (81479) to determine drug metabolizer status is considered **investigational** 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 (81227) to determine drug metabolizer status is considered **medically necessary** when:

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

1. Siponimod[1] (e.g., Mayzent), **OR**

2. Celecoxib[2] (e.g., Celebrex, Elyxyb), **OR**

3. Dronabinol[3] (e.g., Marinol, Syndros), **OR**

4. Erdafitinib[4] (e.g., Balversa), **OR**
5. Flurbiprofen[5] (e.g., Ansaid), **OR**
6. Fosphenytoin[6] (e.g., Cerebyx, Sesquient), **OR**
7. Meloxicam[7] (e.g., Anjeso, Mobic, Vivlodex, Qmiiz ODT), **OR**
8. Nateglinide[8] (e.g., Starlix), **OR**
9. Phenytoin[9] (e.g., Dilantin, Phenytek), **OR**
10. Piroxicam[10] (e.g., Feldene), **OR**
11. Warfarin[11] (e.g., Coumadin, Jantoven).

II. *CYP2C9* variant analysis (81227) to determine drug metabolizer status is considered **investigational** 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 (81225) to determine drug metabolizer status is considered **medically necessary** when:
   A. The member is being considered for or is currently undergoing treatment with any of the following:
      1. Clopidogrel[1] (e.g., Plavix) **OR**
      2. Abrocitinib[2] (e.g., Cibinqo), **OR**
      3. Belzutifan[3] (e.g., Welireg), **OR**
      4. Brivaracetam[4] (e.g., Briviact, Brivajoy), **OR**
      5. Citalopram[5] (e.g., Celexa), **OR**
      6. Cobazam[6] (e.g., Onfi), **OR**
      7. Flibanserin[7] (e.g., Addyi), **OR**
      8. Pantoprazole[8] (e.g., Protonix).

II. *CYP2C19* variant analysis (81225) to determine drug metabolizer status is considered **investigational** for all other indications.

[1] Commonly prescribed after a 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 (81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) to determine drug metabolizer status is considered **medically necessary** when:
   A. The member is being considered for or is currently undergoing treatment with any of the following:
      1. Eliglustat[1] (e.g., Cerdelga), **OR**
      2. Tetrabenazine[2] (e.g., Xenazine), **OR**
      3. Amphetamine[3] (e.g., Adzenys, Dyanavel, Evekeo), **OR**
      4. Aripiprazole[4] (e.g., Abilify, Abilify Maintena), **OR**
      5. Aripiprazole lauroxil[5] (e.g., Aristada), **OR**
      6. Atomoxetine[6] (e.g., Strattera), **OR**
      7. Brexpiprazole[7] (e.g., Rexulti), **OR**
      8. Clozapine[8] (e.g., Versacloz, FazaClo, Clozaril), **OR**
      9. Deutetrabenazine[9] (e.g., Austedo), **OR**
      10. Gefitinib[10] (e.g., Iressa), **OR**
      11. Iloperidone[11] (e.g., Fanapt), **OR**
      12. Lofexidine[12] (e.g., Lucemyra), **OR**
      13. Meclizine[13] (e.g., Antivert, Bonine, Dramamine, Verticalm, Zentrip), **OR**
      14. Metoclopramide[14] (e.g., Reglan, Metozolv), **OR**
      15. Oliceridine[15] (e.g., Olinvyk), **OR**
      16. Pimozide[16] (e.g., Orap), **OR**
      17. Pitolisant[17] (e.g., Wakix), **OR**
      18. Propafenone[18] (e.g., Rythmol), **OR**
      19. Thioridazine[19] (e.g., Mellaril), **OR**

20. Tramadol[20] (e.g., ConZip, Ultram), **OR**

21. Valbenazine[21] (e.g., Ingrezza), **OR**

22. Venlafaxine[22] (e.g., Effexor), **OR**

23. Vortioxetine[23] (e.g., Trintellix, Brintellix), **OR**

24. Codeine[24].

II. *CYP2D6* variant analysis (81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) to determine drug metabolizer status is considered **investigational** 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 (81231) to determine drug metabolizer status is considered **medically necessary** when:

A. The member is being considered for or is currently undergoing treatment with tacrolimus[1] (e.g., Protopic, Envarsus, Astagraf, Prograf).

II. *CYP3A5* variant analysis (81231) to determine drug metabolizer status is considered **investigational** 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 (81479) to determine drug metabolizer status is considered **medically necessary** when:

A. The member is being considered for or is currently undergoing treatment with warfarin[1] (e.g., Coumadin, Jantoven).

II. *CYP4F2* variant analysis (81479) to determine drug metabolizer status is considered **investigational** 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 (81232) to determine drug metabolizer status is considered **medically necessary** when:

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

1. Fluorouracil[1] (e.g., Carac, Efudex, Tolak, Fluoroplex), **OR**

2. Capecitabine[1] (e.g., Xeloda).

II. *DPYD* variant analysis (81232) to determine drug metabolizer status is considered **investigational** 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 (81379, 81380, 81381) is considered **medically necessary** when the member meets the following:

A. The member is age 18 or older, **AND**

B. The member has a diagnosis of one of the following:

1. Metastatic uveal melanoma, **OR**

2. Unresectable uveal melanoma, **AND**

C. The member has not had rapid progression of disease.

II. *HLA-A*02:01* variant analysis (81379, 81380, 81381) is considered **investigational** for all other indications.

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*HLA-B*15:02* Variant Analysis

I. *HLA-B*15:02* variant analysis (81381) to determine drug metabolizer status is considered **medically necessary** when:

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

1. Carbamazepine containing therapy[1] (e.g., Tegretol, Carbatrol, Epitol, Equetro), **OR**

2. Phenytoin[2] (e.g., Dilantin, Phenytek), **OR**

3. Fosphenytoin[2] (e.g., Cerebyx, Sesquient).

II. *HLA-B*15:02* variant analysis (81381) to determine drug metabolizer status is considered **investigational** 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 (81381) to determine drug metabolizer status is considered **medically necessary** when:

A. The member is being considered for or is currently undergoing treatment with abacavir[1] (e.g., Ziagen).

II. *HLA-B*57:01* variant analysis (81381) to determine drug metabolizer status is considered **investigational** for all other indications.

[1] Commonly prescribed for individuals with HIV

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NAT2 Variant Analysis

I. *NAT2* variant analysis (81479) to determine drug metabolizer status is considered **medically necessary** when:

A. The member is being considered for or is currently undergoing treatment with

amifampridine/amifampridine phosphate[1] (e.g., Firdapse, Ruzurgi).

II. *NAT2* variant analysis (81479) to determine drug metabolizer status is considered **investigational** for all other indications.

[1] Commonly prescribed for treatment of Lambert-Eaton myasthenic syndrome

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TPMT and *NUDT15* Variant Analysis

I. *TMPT* and *NUDT15* variant analysis (81306, 81335, 0034U, 0169U) to determine drug metabolizer status is considered **medically necessary** when:

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

1. Azathioprine[1] (e.g., Imuran and Azasan), **OR**
2. Mercaptopurine[2] (e.g., Purinethol and Purixan), **OR**
3. Thioguanine[3] (e.g., Tabloid), **OR**

B. The member is on thiopurine therapy, **AND**

1. The member has had abnormal complete blood count results that do not respond to dose reduction.

II. *TPMT* and *NUDT15* variant analysis (81306, 81335, 0034U, 0169U) to determine drug metabolizer status is considered **investigational** 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 (81350) to determine drug metabolizer status is considered **medically necessary** when:

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

1. Irinotecan[1] (e.g., Onivyde, Camptosar), **OR**
2. Belinostat[2] (e.g., Beleodaq), **OR**
3. Sacituzumab govitecan-hziy[3] (e.g., Trodelvy).

II. *UGT1A1* variant analysis (81350) to determine drug metabolizer status is considered **investigational** 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 (81479) to determine drug metabolizer status is **medically necessary** when:

   A. The member is being considered for or is currently undergoing treatment with belzutifan[1] (e.g., Welireg).

II. *UGT2B17* variant analysis (81479) to determine drug metabolizer status is considered **investigational** 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 (81355) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member is being considered for or is currently undergoing treatment with warfarin[1] (e.g., Coumadin, Jantoven).

II. *VKORC1* variant analysis (81355) to determine drug metabolizer status is considered **investigational** for all other indications.

[1] Commonly prescribed to reduce the formation of blood clots

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Warfarin Sensitivity Analysis Panels

I. Multigene panel analysis to determine drug metabolizer status for warfarin[1] sensitivity (81227, 81355, 0030U) is considered **medically necessary** when:

   A. The member is being considered for or is undergoing treatment with warfarin, **AND**

      1. The member has not reached a therapeutic dose, **AND**

   B. The member is undergoing prophylaxis and treatment of venous thrombosis or pulmonary embolism, **OR**

   C. The member is undergoing prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, **OR**

   D. The member has a history of previous myocardial infarction.

II. Multigene panel analysis to confirm drug metabolizer status for warfarin[1] sensitivity (81227, 81355, 0030U) is considered **investigational** for all other indications.

[1] Commonly prescribed to reduce the formation of blood clots

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Other Pharmacogenetic Single Gene Variant Analysis

I. Variant analysis of all other genes for drug metabolizer status is considered **investigational**, 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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PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

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
2. **Clinical utility** refers to the risks and benefits resulting from genetic test use. The most important considerations in determining clinical utility are: (1) whether the test and any subsequent interventions lead to an improved health outcome among people with a positive test result; and (2) what risks occur as a result of testing.

BACKGROUND AND RATIONALE

Pharmacogenetic Panel Testing

There are no professional society guidelines that address the clinical utility of large pharmacogenetic testing panels for the general population or for a specific population. The US Food and Drug Administration (FDA) also does not address the usage of pharmacogenetic panels.

There are several recent studies that investigated the usefulness of pharmacogenetic panels [for example, Greden et al (2019), Perlis et al (2020), Shan et al (2019), Tiwari et al (2022), Oslin (2022)]. However, these studies had different designs and often conflicting results regarding clinical utility, making it difficult to determine whether there is clinical utility for these types of tests.

A rapid review and meta-analysis by Bunka et al (2023) of 10 randomized controlled trials to

evaluate pharmacogenomic-guided care for major depression showed that, while there is likely beneficial effects to adults with moderate to severe major depressive disorder utilizing pharmacogenomic panels, there is “very low certainty in the magnitude of effect.” (p. 1) This analysis also noted the “high risk of bias and inconsistency between trials.” (p. 1)

There are several single gene pharmacogenetic tests in which the FDA describes the clinical utility of the test results for a given gene/drug/testing indication. These are outlined below.

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.

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.

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
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

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
			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.

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,

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
			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.

CYP2D6 Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (4.2024) 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.

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
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.

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
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.

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Vortioxetine	CYP2D6	poor metabolizers	Results in higher systemic concentrations. The maximum recommended dose is 10 mg.

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.

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.

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.

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)

“Treat patients until unacceptable toxicity or disease progression occur.” (p. 2)

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“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)

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.

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.

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
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.

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.

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
			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

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
			metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for acute lymphoblastic leukemia (2.2024) recommends that, for patients receiving treatment with 6-MP, testing for *TPMT* gene polymorphisms is recommended for patients who develop severe neutropenia after starting 6-MP. (p. ALL-D 1A, p. ALL-D 2A, p. ALL-D 3A, p. ALL-D 9A)

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.

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.

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.

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.

Other 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").

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Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

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