Concert Genetics Genetic Testing: Pharmacogenetics

Reference Number: LA.CP.CG.26 Coding implications
Date of Last Revision 0~~1~~6/25~~4~~
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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

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 2023, 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 and may not support medical necessity. 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 ~~and,~~ associated laboratories ~~and,~~ CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the ~~Concert Genetics Platform~~Concert Platform for a comprehensive list of registered tests.

NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for

members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.

~~Criteria Sections~~Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	~~Ref~~Ref
~~Pharmacogenetic Panel Tests~~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*, ~~0348U*,~~ ~~0349U*,~~ ~~0350U*~~		
	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,	0173U*		

	(RPRD Diagnostics)			
	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* Variant Analysis	BCHE Single Gene Test (Blueprint Genetics)	81479	Z01.81, Z01.810, Z01.811, Z01.818, Z01.89	8

~~*CYP2C9* Variant Analysis~~*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* 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* 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~~ CYP2D6 Nonduplicated Gene Analysis (Mayo Clinic Laboratories)	0074U*		
	CYP2D6 5' gene duplication/multiplication targeted sequence analysis (Mayo Clinic Laboratories)	0075U*		
	CYP2D6 3' gene duplication/multiplication targeted sequence analysis (Mayo Clinic	0076U*		

	Laboratories)			
~~*CYP3A5* Variant Analysis~~*CYP3A5* Variant Analysis	~~CYP3A5 single gene test (Blueprint Genetics)~~Pain Management, CYP450 3A5 Genotype, Qualitative (Quest Diagnostics)	81231*	T86, Z79.6, Z94	8
~~*CYP4F2* Variant Analysis~~*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* Variant Analysis	~~DPD 5-Fluorouracil Toxicity~~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) HLA-A*02:01-Specific (LabCorp) HLA-A*02:01 Determination (Versiti)	81379*, 81380*, 81381*	C69, C69.4	11, 12
~~*HLA-B**15:02 Variant Analysis~~*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 Variant Analysis	HLA B*57:01 Abacavir Hypersensitivity (Labcorp)	81381*	B20, Z21	8
~~*NAT2* Variant Analysis~~*NAT2* Variant Analysis	NAT2 single gene test (Blueprint Genetics)	81479	G73, M35.9	8
~~*TPMT* and~~	Thiopurine S-	81335*	C91.0, K50.00-K50.90	8, 10

~~*NUDT15* Variant Analysis~~*TPMT* and *NUDT15* Variant Analysis	Methyltransferase (*TPMT*) Genotype (Quest Diagnostics)		K51.00-K51.319, M35.9, M05-M06.9, C85.90	
	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 Irinotecan Toxicity (Labcorp)	81350*	B20, C18, C19, C20, C50, C84, E80.4	8
~~*UGT1A1* Variant Analysis~~*UGT1A1* Variant Analysis				
~~*UGT2B17* Variant Analysis~~*UGT2B17* Variant Analysis	UGT2B17 Single Gene (Fulgent Genetics)	81479	C25, C64, C71, C72, Q85.83	8
~~*VKORC1* Variant Analysis~~*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 Sensitivity Analysis Panels	Warfarin Response Genotype (Mayo Medical Laboratories)	0030U*	I21, I26, I48	8, 9
	Accutype Warfarin (Quest)	81227*, 81355*		
~~Other Single Gene Variant Analysis~~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	

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

~~back to top~~back to top

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

I. The use of pharmacogenetic testing panels (81418, 0029U, 0033U, 0173U, 0175U, 0286U, 0345U, 0347U, 0348U, 0349U, 0350U, 0380U, 0392U, 0411U, 0419U, 0423U, 0434U, 0438U, 0460U, 0461U) is considered **investigational*** for all indications.

~~*See *HLA-B**15:02 and *HLA-A**31:01 Variant Analysis and~~*See *TPMT* and *NUDT15* Variant Analysis below for criteria. ~~These tests involve~~This test involves analysis of more than one gene, but ~~are~~is not considered experimental/investigational as a panel ("panel" defined as a genetic test analyzing more than one gene)

~~back to top~~

back to top

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/enrollee 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.

~~back to top~~

back to top

CYP2C9 Variant Analysis

I. *CYP2C9* variant analysis (81227) 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. 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

~~back to top~~

back to top

CYP2C19 Variant Analysis

I. *CYP2C19* variant analysis (81225) 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. Clopidogrel[1] (e.g., Plavix~~), AND~~) **OR**

~~a) The member/enrollee meets all of the following:~~

~~(1) Will be undergoing percutaneous coronary intervention (PCI), AND~~

~~(2) Has acute coronary syndromes (ACS), AND~~

~~(3) Is at high risk for poor outcomes (e.g., urgent PCI for an ACS event, elective PCI for unprotected left main disease or last patent coronary artery), 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

~~back to top~~

back to top

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/enrollee 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. ~~T~~ 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

~~back to top~~

back to top

CYP3A5 Variant Analysis

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

   A. The member/enrollee 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

~~back to top~~

back to top

CYP4F2 Variant Analysis

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

A. The member/enrollee 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

~~back to top~~

back to top

DPYD Variant Analysis

I. *DPYD* variant analysis (81232) 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. Fluorouracil[1] (e.g., ~~Adrucil~~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

~~back to top~~

back to top

*HLA-A*02:01* Variant Analysis

I. *HLA-A*02:01* variant analysis (81379, 81380, 81381) 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, **AND**

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

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

back to top

*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/enrollee 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

~~back to top~~

back to top

*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/enrollee 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

~~back to top~~

back to top

NAT2 Variant Analysis

I. *NAT2* variant analysis (81479) 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 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

~~back to top~~back to top

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/enrollee 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/enrollee is on thiopurine therapy ~~and~~, **AND**

~~4.~~1. The member/enrollee 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

~~back to top~~

back to top

UGT1A1 Variant Analysis

I. *UGT1A1* variant analysis (81350) 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. 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 ~~and~~, rectal and pancreatic cancers

[2] Commonly prescribed for treatment of peripheral T-cell lymphoma

[3] Commonly prescribed for treatment of breast and urothelial cancers

~~back to top~~

back to top

UGT2B17 Variant Analysis

I. *UGT2B17* variant analysis (81479) to determine drug metabolizer status is **medically necessary** when:

   A. The member/enrollee 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

~~back to top~~

back to top

VKORC1 Variant Analysis

I. *VKORC1* variant analysis (81355) to determine drug metabolizer status is considered **medically necessary** when:

   A. The member/enrollee 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

~~back to top~~

back to top

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/enrollee is being considered for or is undergoing treatment with warfarin, **AND**

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

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

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

C.D. The member/enrollee has a history of previous myocardial infarction, **AND**.

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

The member/enrollee has not reached a therapeutic dose.

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

back to top

back to top

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)
A. *SLCO1B1* (81328)
E. *TYMS* (81479)).

back to top

back to top

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	Results in higher systemic concentrations and

		metabolizers	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.
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.

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.

CYP2D6 Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (~~1~~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.
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.

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)

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)

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. 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.

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, ~~SLCO1B1,~~* or *TYMS* in Section 1 of the Table of Pharmacogenetic Associations ("Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations").

~~back to top~~back to top

Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
Converted corporate policy to local policy	1/24	2/27/24	
Semi-annual review. 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.	06/24	9/4/24	10/4/24

~~References~~

Semi-annual review. Updated title to reflect V1.2024. Renamed to Concert Genetics Pharmacogenetic Testing (Version A). Pharmacogenetic Panel Tests: Added new PLA codes 0476U, 0477U, 0516U to the policy reference table due to AMA code release; separated some PLA codes into separate lines in the policy reference table; deleted reference in footnote to a specific criteria set that no longer exists in this policy; added new PLA codes to Policy Reference Table. 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. 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 based on client request.	1/25		

REFERENCES

1. Greden JF, Parikh SV, Rothschild AJ, et al. Impact of pharmacogenomics clinical outcomes major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res. 2019;111:59-67. doi:10.1016/j.jpsychires.2019.01.003
2. Perlis RH, Dowd D,Fava M, Lencz T, Krause DS. Randomized,controlled, participant- and rater-blind trial of pharmacogenomic test-guided treatment versus treatment as usual for major depressive disorder. Depress Anxiety. 2020;37(9): 834-841. doi:10.1002/da.23029
3. Shan X, Zhao W, Qiu Y,et al. Preliminary clinical investigation of combinatorial pharmacogenomic testing for the optimized treatment of depression: a randomized single-blind study. Front Neurosci. 2019;13:960. doi:10.3389/fnins.2019.00960
4. Tiwari AK, Zai CC, Altar CA, et al. Clinical utility of combinatorial pharmacogenomic testing in depression: a Canadian patient- and rater-blinded, randomized, controlled trial. Transl Psychiatry. 2022;12(1):101. doi:10.1038/s41398-022-01847-8
5. Oslin DW, Lynch KG, Shih MC, et al. Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder: The PRIME Care Randomized Clinical Trial. JAMA. 2022;328(2):151-161. doi:10.1001/jama.2022.9805
6. Bunka M, Wong G, Kim D, et al. Evaluating treatment outcomes in pharmacogenomic-guided care for major depression: A rapid review and meta-analysis. Psychiatry Res. 2023;321:115102.
7. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version ~~1~~4.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
8. Table of Pharmacogenetic Associations. (2022, October 26). FDA. https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations. Accessed ~~April 28, 2023~~June 5, 2024.
9. Bristol-Myers Squibb Company. Coumadin (warfarin sodium).- U.S. Food and Drug Administration. Website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf. Accessed 12/5/2023.

10. ~~back to top~~National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines for Oncology: Acute Lymphoblastic Leukemia. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf
11. Chen LN, Carvajal RD. Tebentafusp for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. Expert Rev Anticancer Ther. 2022 Oct;22(10):1017-1027. doi: 10.1080/14737140.2022.2124971. Epub 2022 Sep 19. PMID: 36102132; PMCID: PMC10184536.

Immunocore Limited. KIMMTRAK (tebentafusp-tebn) injection. U.S. Food and Drug Administration. Accessed: 5/8/2024. Website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761228s000lbl.pdf

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. LHCC 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.

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 LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC 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 LHCC has no control or right of control. Providers are not agents or employees of LHCC.

This clinical policy is the property of LHCC. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers,

member/enrollees, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, member/enrollees and their representatives agree to be bound by such terms and conditions by providing services to member/enrollees and/or submitting claims for payment for such services.

back to top