BSC_CON_2.12	Genetic Testing: Pharmacogenetics		
Original Policy Date:	February 1, 2024	**Effective Date:**	November 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 35

Example Test 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. Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Pharmacogenetic Panel Tests	GeneSight Psychotropic (Myriad Genetics)	0345U
	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)	0347U, 0348U, 0349U, 0350U
	Focused Pharmacogenomics Panel (Mayo Clinic Laboratories)	0029U
	Psych HealthPGx Panel, (RPRD Diagnostics)	0173U
	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
Pharmacogenetic Single Gene Tests		
BCHE Variant Analysis	BCHE Single Gene Test (Blueprint Genetics)	81479
CYP2C9 Variant Analysis	Cytochrome P450 2C9 Genotype (Quest Diagnostics)	81227

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
CYP2C19 Variant Analysis	CYP2C19 Single Gene Test (Blueprint Genetics)	81225
CYP2D6 Variant Analysis	CYP2D6 (ARUP Laboratories)	81226
	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 Laboratories)	0076U
CYP3A5 Variant Analysis	CYP3A5 single gene test (Blueprint Genetics)	81231
CYP4F2 Variant Analysis	CYP4F2 Single Gene Test (Blueprint Genetics)	81479
DPYD Variant Analysis	DPD 5-Fluorouracil Toxicity (Labcorp)	81232
*HLA-B**15:02 Variant Analysis	HLA-B*15:02, Carbamazepine Sensitivity (Labcorp)	81381
*HLA-B**57:01 Variant Analysis	HLA B*57:01 Abacavir Hypersensitivity (Labcorp)	81381
NAT2 Variant Analysis	NAT2 single gene test (Blueprint Genetics)	81479
TPMT and *NUDT15* Variant Analysis	Thiopurine S-Methyltransferase (*TPMT*) Genotype (Quest Diagnostics)	81335
	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 Irinotecan Toxicity (Labcorp)	81350
UGT1A1 Variant Analysis		
UGT2B17 Variant Analysis	UGT2B17 Single Gene (Fulgent Genetics)	81479
VKORC1 Variant Analysis	VKORC1 Single Gene Test (Blueprint Genetics)	81355

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Warfarin Sensitivity Analysis Panels	Warfarin Response Genotype (Mayo Medical Laboratories)	0030U
	Accutype Warfarin (Quest)	81227, 81355
Other Single Gene Variant Analysis	Catechol-O-Methyltransferase (COMT) Genotype (Mayo Clinic Laboratories)	0032U
	COMT single gene test (Blueprint Genetics)	81479
	Cytochrome P450 1A2 Genotype (Mayo Clinic Laboratories)	0031U
	CYP1A2 single gene test (Blueprint Genetics)	81479
	Cardio IQ KIF6 Genotype (Quest Diagnostics)	81479
	Opioid Receptor, mu OPRM1 Genotype, 1 Variant (ARUP Laboratories)	81479
	SLCO1B1, 1 Variant (ARUP Laboratories)	81328
	TYMS Single Gene (Sequencing & Deletion/Duplication) (Fulgent Genetics)	81479

Policy Statement

Pharmacogenetic Panel Tests

I. Pharmacogenetic panel tests (0345U, 0175U, 0029U, 0380U, 0411U, 0419U, 81418, 81479) may be considered **medically necessary** when **all** of the following are met:
   A. The member is age 18 years or older
   B. The member has a diagnosis of **any** of the following for which a treatment medication is being considered:
      1. Major depressive disorder
      2. Generalized anxiety disorder
   C. The member has failed at least one medication intended to treat their condition
   D. The member is being considered for one or more specific medication(s) related to their diagnosis that is known to have a gene-drug interaction
   E. The pharmacogenetic panel test being considered has proven clinical validity,
   F. The pharmacogenetic panel test being considered has proven clinical utility.

II. Pharmacogenetic panel tests (0345U, 0175U, 0029U, 0380U, 0411U, 0419U, 81418, 81479) are considered **investigational** for all other indications, including as an initial screening test for medication selection.

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

Pharmacogenetic Single Gene Tests

BCHE Variant Analysis

III. *BCHE* variant analysis (81479) to determine drug metabolizer status may be 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)
   2. Succinylcholine[1] (e.g., Anectine, Suxamethonium).

IV. *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.

CYP2C9 Variant Analysis

V. *CYP2C9* variant analysis (81227) to determine drug metabolizer status may be 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)
      2. Celecoxib[2] (e.g., Celebrex, Elyxyb)
      3. Dronabinol[3] (e.g., Marinol, Syndros)
      4. Erdafitinib[4] (e.g., Balversa)
      5. Flurbiprofen[5] (e.g., Ansaid)
      6. Fosphenytoin[6] (e.g., Cerebyx, Sesquient)
      7. Meloxicam[7] (e.g., Anjeso, Mobic, Vivlodex, Qmiiz ODT)
      8. Nateglinide[8] (e.g., Starlix)
      9. Phenytoin[9] (e.g., Dilantin, Phenytek)
      10. Piroxicam[10] (e.g., Feldene)
      11. Warfarin[11] (e.g., Coumadin, Jantoven).

VI. *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

CYP2C19 Variant Analysis

VII. *CYP2C19* variant analysis (81225) to determine drug metabolizer status may be 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), **AND**
         a. The member meets **all** of the following:
            i. Will be undergoing percutaneous coronary intervention (PCI)
            ii. Has acute coronary syndromes (ACS)
            iii. 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)
      2. Abrocitinib[2] (e.g., Cibinqo)
      3. Belzutifan[3] (e.g., Welireg)

4. Brivaracetam[4] (e.g., Briviact, Brivajoy)
5. Citalopram[5] (e.g., Celexa)
6. Cobazam[6] (e.g., Onfi)
7. Flibanserin[7] (e.g., Addyi)
8. Pantoprazole[8] (e.g., Protonix).

VIII. *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

CYP2D6 Variant Analysis

IX. *CYP2D6* variant analysis (81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) to determine drug metabolizer status may be 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)
      2. Tetrabenazine[2] (e.g., Xenazine)
      3. Amphetamine[3] (e.g., Adzenys, Dyanavel, Evekeo)
      4. Aripiprazole[4] (e.g., Abilify, Abilify Maintena)
      5. Aripiprazole lauroxil[5] (e.g., Aristada)
      6. T Atomoxetine[6] (e.g., Strattera)
      7. Brexpiprazole[7] (e.g., Rexulti)
      8. Clozapine[8] (e.g., Versacloz, FazaClo, Clozaril)
      9. Deutetrabenazine[9] (e.g., Austedo)
      10. Gefitinib[10] (e.g., Iressa)
      11. Iloperidone[11] (e.g., Fanapt)
      12. Lofexidine[12] (e.g., Lucemyra)
      13. Meclizine[13] (e.g., Antivert, Bonine, Dramamine, Verticalm, Zentrip)
      14. Metoclopramide[14] (e.g., Reglan)
      15. Oliceridine[15] (e.g., Olinvyk)
      16. Pimozide[16] (e.g., Orap)
      17. Pitolisant[17] (e.g., Wakix)
      18. Propafenone[18] (e.g., Rythmol)
      19. Thioridazine[19] (e.g., Mellaril)
      20. Tramadol[20] (e.g., ConZip, Ultram)
      21. Valbenazine[21] (e.g., Ingrezza)
      22. Venlafaxine[22] (e.g., Effexor)
      23. Vortioxetine[23] (e.g., Trintellix, Brintellix)
      24. Codeine[24]

X. *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

CYP3A5 Variant Analysis

XI. *CYP3A5* variant analysis (81231) to determine drug metabolizer status may be 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).

XII. *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

CYP4F2 Variant Analysis

XIII. *CYP4F2* variant analysis (81479) to determine drug metabolizer status may be considered **medically necessary** when:
   A. The member is being considered for or is currently undergoing treatment with warfarin[1] (e.g., Coumadin, Jantoven).

XIV. *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

DPYD Variant Analysis

XV. *DPYD* variant analysis (81232) to determine drug metabolizer status may be 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., Adrucil)

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

XVI. *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

*HLA-B*15:02* Variant Analysis

XVII. *HLA-B*15:02* variant analysis (81381) to determine drug metabolizer status may be 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)
2. Phenytoin[2] (e.g., Dilantin, Phenytek)
3. Fosphenytoin[2] (e.g., Cerebyx, Sesquient).

XVIII. *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

*HLA-B*57:01* Variant Analysis

XIX. *HLA-B*57:01* variant analysis (81381) to determine drug metabolizer status may be considered **medically necessary** when:
A. The member is being considered for or is currently undergoing treatment with abacavir[1] (e.g., Ziagen).

XX. *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

NAT2 Variant Analysis

XXI. *NAT2* variant analysis (81479) to determine drug metabolizer status may be 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).

XXII. *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

TPMT and *NUDT15* Variant Analysis

XXIII. *TMPT* and *NUDT15* variant analysis (81306, 81335, 0034U, 0169U) to determine drug metabolizer status may be 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 Azasa
2. Mercaptopurine[2] (e.g., Purinethol and Purixan)
3. Thioguanine[3] (e.g., Tabloid)

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

XXIV. *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

UGT1A1 Variant Analysis

XXV. *UGT1A1* variant analysis (81350) to determine drug metabolizer status may be 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)
2. Belinostat[2] (e.g., Beleodaq)
3. Sacituzumab govitecan-hziy[3] (e.g., Trodelvy).

XXVI. *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 cancers
[2] Commonly prescribed for treatment of peripheral T-cell lymphoma
[3] Commonly prescribed for treatment of breast and urothelial cancers

UGT2B17 Variant Analysis

XXVII. *UGT2B17* variant analysis (81479) to determine drug metabolizer status may be **medically necessary** when:
A. The member is being considered for or is currently undergoing treatment with belzutifan[1] (e.g., Welireg).

XXVIII. *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

VKORC1 Variant Analysis

XXIX. *VKORC1* variant analysis (81355) to determine drug metabolizer status may be considered **medically necessary** when:
A. The member is being considered for or is currently undergoing treatment with warfarin[1] (e.g., Coumadin, Jantoven).

XXX. *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

Warfarin Sensitivity Analysis Panels

XXXI. Multigene panel analysis to determine drug metabolizer status for warfarin[1] sensitivity (81227, 81355, 0030U) may be considered **medically necessary** when:
A. The member is undergoing prophylaxis and treatment of venous thrombosis or pulmonary embolism, **OR**

B. The member is undergoing prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, **OR**
C. The member has a history of previous myocardial infarction, **AND**
D. The member is being considered for or is undergoing treatment with warfarin, **AND**
   1. The member has not reached a therapeutic dose.

XXXII. 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

Other Single Gene Variant Analysis

XXXIII. 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. *SLCO1B1* (81328)
F. *TYMS* (81479)

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

Coding

See the Codes table for details.

Description

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

has had an adverse drug reaction or to assess response to treatment. Test methodology includes genotyping and single nucleotide variant testing.

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.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

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.
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

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
			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

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
			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 (1.2024) recommend against *CYP2D6* genotype testing for women being considered for tamoxifen treatment. (p. DCIS-2 and p. BINV-K)

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.

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
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.

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
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

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
			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-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.

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
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

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
			(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.

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").

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled "MolDX: Pharmacogenomics Testing" states the following: "PGx tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable…"

The CMS local coverage determination (LCD) reference article entitled "Billing and Coding: MolDX: Pharmacogenomics Testing" lists several panels it considers "covered multigene panels with intended uses" for major depressive disorder (MDD) and several neuropsychiatric disorders. This reference

article also outlines specific multigene panels covered for neuropsychiatric indications, included in the "covered multigene panels with intended uses" table as well as the Group 1 Codes table.

Ghanbarian et al
In the 2023 publication of the results of their microsimulation model of care pathways for major depressive disorder, many characteristics of patients and outcomes were simulated, including the following: "All patients enter the model in the MDD state. After receiving treatment, patients may have an event, such as stopping treatment, remission (full or partial) or recurrence." (p. E1500) Given that *CYP2C19* and *CYP2D6* normal metabolizer phenotypes are the most common in the population, it is reasonable to assume that most individuals will not find benefit from this testing, and those that have failed at least one treatment medication are more likely to have an abnormal metabolizer phenotype.

Bunka et al
A 2023 rapid review and meta-analysis 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) and "evidence was only available for adult patients (with the exception of one recent RCT that failed to demonstrate differences in symptom improvement)." (p.6)

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Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier.
  The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
	0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (i.e., CYP2C9, CYP4F2, VKORC1, rs12777823)

Type	Code	Description
	0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7)
	0032U	COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant
	0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (e.g., citalopram metabolism) gene analysis, common variants (i.e., HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])
	0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15)(e.g., thiopurine metabolism), gene analysis, common variants (i.e., TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)
	0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, common and select rare variants (i.e., *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
	0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
	0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)
	0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
	0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)
	0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)
	0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 3' gene duplication/ multiplication) (List separately in addition to code for primary procedure)
	0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism) gene analysis, common variants
	0173U	Psychiatry (i.e., depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes
	0175U	Psychiatry (e.g., depression, anxiety), genomic analysis panel, variant analysis of 15 genes
	0286U	CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism) gene analysis, common variants
	0345U	Psychiatry (e.g., depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6

Type	Code	Description
	0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
	0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
	0349U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions
	0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
	0380U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype
	0392U	Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug
	0411U	Psychiatry (e.g., depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
	0419U	Neuropsychiatry (e.g., depression, anxiety), genomic sequence analysis panel, variant analysis of 13 genes, saliva or buccal swab, report of each gene phenotype
	0423U	Psychiatry (e.g., depression, anxiety), genomic analysis panel, including variant analysis of 26 genes, buccal swab, report including metabolizer status and risk of drug toxicity by condition ***(Code effective 1/1/2024)***
	0434U	Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes ***(Code effective 1/1/2024)***
	0437U	Psychiatry (anxiety disorders), mRNA, gene expression profiling by RNA sequencing of 15 biomarkers, whole blood, algorithm reported as predictive risk score ***(Code effective 1/1/2024)***
	0438U	Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted gene-drug interactions ***(Code effective 1/1/2024)***
	0460U	Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes ***(Code effective 7/1/2024)***
	0461U	Oncology, pharmacogenomic analysis of single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, whole blood or buccal swab, with variant analysis, including impacted gene-drug interactions and reported phenotypes ***(Code effective 7/1/2024)***
	0516U	Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status ***(Code effective 10/1/2024)***
	81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)

Type	Code	Description
	81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
	81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
	81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7)
	81232	DPYD (dihydropyrimidine dehydrogenase) (e.g., 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (e.g., *2A, *4, *5, *6)
	81306	NUDT15 (nudix hydrolase 15) (e.g., drug metabolism) gene analysis, common variant(s) (e.g., *2, *3, *4, *5, *6)
	81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (e.g., adverse drug reaction), gene analysis, common variant(s) (e.g., *5)
	81335	TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3)
	81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (e.g., drug metabolism, hereditary unconjugated hyperbilirubinemia [Gilbert syndrome]) gene analysis, common variants (e.g., *28, *36, *37)
	81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variant(s) (e.g., -1639G>A, c.173+1000C>T)
	81381	HLA Class I typing, high resolution (i.e., alleles or allele groups); one allele or allele group (e.g., B*57:01P), each
	81418	Drug metabolism (e.g., pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/01/2024	New policy.
03/01/2024	Coding update.
07/01/2024	Policy statement, guidelines and literature updated.
09/01/2024	Coding update.
11/01/2024	Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent

therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Genetic Testing: Pharmacogenetics BSC_CON_2.12 **Policy Statement:** **Pharmacogenetic Panel Tests** I. Pharmacogenetic panel tests (0345U, 0175U, 0029U, 0380U, 0411U, 0419U, 81418, 81479) may be considered **medically necessary** when **all** of the following are met: A. The member is age 18 years or older B. The member has a diagnosis of **any** of the following for which a treatment medication is being considered: 1. Major depressive disorder 2. Generalized anxiety disorder C. The member has failed at least one medication intended to treat their condition D. The member is being considered for one or more specific medication(s) related to their diagnosis that is known to have a gene-drug interaction E. The pharmacogenetic panel test being considered has proven clinical validity, F. The pharmacogenetic panel test being considered has proven clinical utility. II. Pharmacogenetic panel tests (0345U, 0175U, 0029U, 0380U, 0411U, 0419U, 81418, 81479) are considered **investigational** for all other indications, including as an initial screening test for medication selection. *See *HLA-B**15:02 and *HLA-A**31:01 Variant Analysis and *TPMT* and *NUDT15* Variant Analysis below for coverage criteria. These tests involve analysis of more than one gene, but are not considered experimental/investigational as a panel ("panel" defined as a genetic test analyzing more than one gene)	**Genetic Testing: Pharmacogenetics BSC_CON_2.12** **Policy Statement:** **Pharmacogenetic Panel Tests** I. Pharmacogenetic panel tests (0345U, 0175U, 0029U, 0380U, 0411U, 0419U, 81418, 81479) may be considered **medically necessary** when **all** of the following are met: A. The member is age 18 years or older B. The member has a diagnosis of **any** of the following for which a treatment medication is being considered: 1. Major depressive disorder 2. Generalized anxiety disorder C. The member has failed at least one medication intended to treat their condition D. The member is being considered for one or more specific medication(s) related to their diagnosis that is known to have a gene-drug interaction E. The pharmacogenetic panel test being considered has proven clinical validity, F. The pharmacogenetic panel test being considered has proven clinical utility. II. Pharmacogenetic panel tests (0345U, 0175U, 0029U, 0380U, 0411U, 0419U, 81418, 81479) are considered **investigational** for all other indications, including as an initial screening test for medication selection. *See *HLA-B**15:02 and *HLA-A**31:01 Variant Analysis and *TPMT* and *NUDT15* Variant Analysis below for coverage criteria. These tests involve analysis of more than one gene, but are not considered experimental/investigational as a panel ("panel" defined as a genetic test analyzing more than one gene)

Pharmacogenetic Single Gene Tests

***BCHE* Variant Analysis**

III. *BCHE* variant analysis (81479) to determine drug metabolizer status may be 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)
      2. Succinylcholine[1] (e.g., Anectine, Suxamethonium).

IV. *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.

***CYP2C9* Variant Analysis**

V. *CYP2C9* variant analysis (81227) to determine drug metabolizer status may be 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)
      2. Celecoxib[2] (e.g., Celebrex, Elyxyb)
      3. Dronabinol[3] (e.g., Marinol, Syndros)
      4. Erdafitinib[4] (e.g., Balversa)
      5. Flurbiprofen[5] (e.g., Ansaid)
      6. Fosphenytoin[6] (e.g., Cerebyx, Sesquient)
      7. Meloxicam[7] (e.g., Anjeso, Mobic, Vivlodex, Qmiiz ODT)
      8. Nateglinide[8] (e.g., Starlix)
      9. Phenytoin[9] (e.g., Dilantin, Phenytek)
      10. Piroxicam[10] (e.g., Feldene)
      11. Warfarin[11] (e.g., Coumadin, Jantoven).

VI. *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

Pharmacogenetic Single Gene Tests

***BCHE* Variant Analysis**

III. *BCHE* variant analysis (81479) to determine drug metabolizer status may be 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)
      2. Succinylcholine[1] (e.g., Anectine, Suxamethonium).

IV. *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.

***CYP2C9* Variant Analysis**

V. *CYP2C9* variant analysis (81227) to determine drug metabolizer status may be 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)
      2. Celecoxib[2] (e.g., Celebrex, Elyxyb)
      3. Dronabinol[3] (e.g., Marinol, Syndros)
      4. Erdafitinib[4] (e.g., Balversa)
      5. Flurbiprofen[5] (e.g., Ansaid)
      6. Fosphenytoin[6] (e.g., Cerebyx, Sesquient)
      7. Meloxicam[7] (e.g., Anjeso, Mobic, Vivlodex, Qmiiz ODT)
      8. Nateglinide[8] (e.g., Starlix)
      9. Phenytoin[9] (e.g., Dilantin, Phenytek)
      10. Piroxicam[10] (e.g., Feldene)
      11. Warfarin[11] (e.g., Coumadin, Jantoven).

VI. *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

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
[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	[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
***CYP2C19* Variant Analysis** VII. *CYP2C19* variant analysis (81225) to determine drug metabolizer status may be 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), **AND** a. The member meets **all** of the following: i. Will be undergoing percutaneous coronary intervention (PCI) ii. Has acute coronary syndromes (ACS) iii. 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) 2. Abrocitinib[2] (e.g., Cibinqo) 3. Belzutifan[3] (e.g., Welireg) 4. Brivaracetam[4] (e.g., Briviact, Brivajoy) 5. Citalopram[5] (e.g., Celexa) 6. Cobazam[6] (e.g., Onfi) 7. Flibanserin[7] (e.g., Addyi) 8. Pantoprazole[8] (e.g., Protonix). VIII. *CYP2C19* variant analysis (81225) to determine drug metabolizer status is considered **investigational** for all other indications.	***CYP2C19* Variant Analysis** VII. *CYP2C19* variant analysis (81225) to determine drug metabolizer status may be 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), **AND** a. The member meets **all** of the following: i. Will be undergoing percutaneous coronary intervention (PCI) ii. Has acute coronary syndromes (ACS) iii. 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) 2. Abrocitinib[2] (e.g., Cibinqo) 3. Belzutifan[3] (e.g., Welireg) 4. Brivaracetam[4] (e.g., Briviact, Brivajoy) 5. Citalopram[5] (e.g., Celexa) 6. Cobazam[6] (e.g., Onfi) 7. Flibanserin[7] (e.g., Addyi) 8. Pantoprazole[8] (e.g., Protonix). VIII. *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	[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

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
[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	[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
***CYP2D6* Variant Analysis** IX. *CYP2D6* variant analysis (81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) to determine drug metabolizer status may be 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) 2. Tetrabenazine[2] (e.g., Xenazine) 3. Amphetamine[3] (e.g., Adzenys, Dyanavel, Evekeo) 4. Aripiprazole[4] (e.g., Abilify, Abilify Maintena) 5. Aripiprazole lauroxil[5] (e.g., Aristada) 6. T Atomoxetine[6] (e.g., Strattera) 7. Brexpiprazole[7] (e.g., Rexulti) 8. Clozapine[8] (e.g., Versacloz, FazaClo, Clozaril) 9. Deutetrabenazine[9] (e.g., Austedo) 10. Gefitinib[10] (e.g., Iressa) 11. Iloperidone[11] (e.g., Fanapt) 12. Lofexidine[12] (e.g., Lucemyra) 13. Meclizine[13] (e.g., Antivert, Bonine, Dramamine, Verticalm, Zentrip) 14. Metoclopramide[14] (e.g., Reglan) 15. Oliceridine[15] (e.g., Olinvyk) 16. Pimozide[16] (e.g., Orap) 17. Pitolisant[17] (e.g., Wakix) 18. Propafenone[18] (e.g., Rythmol) 19. Thioridazine[19] (e.g., Mellaril) 20. Tramadol[20] (e.g., ConZip, Ultram) 21. Valbenazine[21] (e.g., Ingrezza) 22. Venlafaxine[22] (e.g., Effexor) 23. Vortioxetine[23] (e.g., Trintellix, Brintellix) 24. Codeine[24]	***CYP2D6* Variant Analysis** IX. *CYP2D6* variant analysis (81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U) to determine drug metabolizer status may be 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) 2. Tetrabenazine[2] (e.g., Xenazine) 3. Amphetamine[3] (e.g., Adzenys, Dyanavel, Evekeo) 4. Aripiprazole[4] (e.g., Abilify, Abilify Maintena) 5. Aripiprazole lauroxil[5] (e.g., Aristada) 6. T Atomoxetine[6] (e.g., Strattera) 7. Brexpiprazole[7] (e.g., Rexulti) 8. Clozapine[8] (e.g., Versacloz, FazaClo, Clozaril) 9. Deutetrabenazine[9] (e.g., Austedo) 10. Gefitinib[10] (e.g., Iressa) 11. Iloperidone[11] (e.g., Fanapt) 12. Lofexidine[12] (e.g., Lucemyra) 13. Meclizine[13] (e.g., Antivert, Bonine, Dramamine, Verticalm, Zentrip) 14. Metoclopramide[14] (e.g., Reglan) 15. Oliceridine[15] (e.g., Olinvyk) 16. Pimozide[16] (e.g., Orap) 17. Pitolisant[17] (e.g., Wakix) 18. Propafenone[18] (e.g., Rythmol) 19. Thioridazine[19] (e.g., Mellaril) 20. Tramadol[20] (e.g., ConZip, Ultram) 21. Valbenazine[21] (e.g., Ingrezza) 22. Venlafaxine[22] (e.g., Effexor) 23. Vortioxetine[23] (e.g., Trintellix, Brintellix) 24. Codeine[24]

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
X. *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.	X. *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	[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

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
[24] Commonly prescribed for treatment of mild to moderately severe pain, and to help reduce coughing	[24] Commonly prescribed for treatment of mild to moderately severe pain, and to help reduce coughing
***CYP3A5* Variant Analysis** XI. *CYP3A5* variant analysis (81231) to determine drug metabolizer status may be 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). XII. *CYP3A5* variant analysis (81231) to determine drug metabolizer status is considered **investigational** for all other indications.	***CYP3A5* Variant Analysis** XI. *CYP3A5* variant analysis (81231) to determine drug metabolizer status may be 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). XII. *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	[1] Commonly prescribed to individuals who have undergone a heart, kidney, liver, or lung transplant
***CYP4F2* Variant Analysis** XIII. *CYP4F2* variant analysis (81479) to determine drug metabolizer status may be considered **medically necessary** when: A. The member is being considered for or is currently undergoing treatment with warfarin[1] (e.g., Coumadin, Jantoven). XIV. *CYP4F2* variant analysis (81479) to determine drug metabolizer status is considered **investigational** for all other indications.	***CYP4F2* Variant Analysis** XIII. *CYP4F2* variant analysis (81479) to determine drug metabolizer status may be considered **medically necessary** when: A. The member is being considered for or is currently undergoing treatment with warfarin[1] (e.g., Coumadin, Jantoven). XIV. *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	[1] Commonly prescribed to reduce the formation of blood clots
***DPYD* Variant Analysis** XV. *DPYD* variant analysis (81232) to determine drug metabolizer status may be 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., Adrucil) 2. Capecitabine[1] (e.g., Xeloda). XVI. *DPYD* variant analysis (81232) to determine drug metabolizer status is considered **investigational** for all other indications.	***DPYD* Variant Analysis** XV. *DPYD* variant analysis (81232) to determine drug metabolizer status may be 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., Adrucil) 2. Capecitabine[1] (e.g., Xeloda). XVI. *DPYD* variant analysis (81232) to determine drug metabolizer status is considered **investigational** for all other indications.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
[1] Commonly prescribed for individuals diagnosed with colorectal, breast, and aerodigestive tract tumors	[1] Commonly prescribed for individuals diagnosed with colorectal, breast, and aerodigestive tract tumors
***HLA-B*15:02* Variant Analysis** XVII. *HLA-B*15:02* variant analysis (81381) to determine drug metabolizer status may be 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) 2. Phenytoin[2] (e.g., Dilantin, Phenytek) 3. Fosphenytoin[2] (e.g., Cerebyx, Sesquient). XVIII. *HLA-B*15:02* variant analysis (81381) to determine drug metabolizer status is considered **investigational** for all other indications.	***HLA-B*15:02* Variant Analysis** XVII. *HLA-B*15:02* variant analysis (81381) to determine drug metabolizer status may be 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) 2. Phenytoin[2] (e.g., Dilantin, Phenytek) 3. Fosphenytoin[2] (e.g., Cerebyx, Sesquient). XVIII. *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	[1] Commonly prescribed for individuals with epilepsy, trigeminal neuralgia, or bipolar disorder [2] Commonly prescribed for treatment of seizures
***HLA-B*57:01* Variant Analysis** XIX. *HLA-B*57:01* variant analysis (81381) to determine drug metabolizer status may be considered **medically necessary** when: A. The member is being considered for or is currently undergoing treatment with abacavir[1] (e.g., Ziagen). XX. *HLA-B*57:01* variant analysis (81381) to determine drug metabolizer status is considered **investigational** for all other indications.	***HLA-B*57:01* Variant Analysis** XIX. *HLA-B*57:01* variant analysis (81381) to determine drug metabolizer status may be considered **medically necessary** when: A. The member is being considered for or is currently undergoing treatment with abacavir[1] (e.g., Ziagen). XX. *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	[1] Commonly prescribed for individuals with HIV
***NAT2* Variant Analysis** XXI. *NAT2* variant analysis (81479) to determine drug metabolizer status may be considered **medically necessary** when:	***NAT2* Variant Analysis** XXI. *NAT2* variant analysis (81479) to determine drug metabolizer status may be considered **medically necessary** when:

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
A. The member is being considered for or is currently undergoing treatment with amifampridine/amifampridine phosphate[1] (e.g., Firdapse, Ruzurgi).	A. The member is being considered for or is currently undergoing treatment with amifampridine/amifampridine phosphate[1] (e.g., Firdapse, Ruzurgi).
XXII. *NAT2* variant analysis (81479) to determine drug metabolizer status is considered **investigational** for all other indications.	XXII. *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	[1] Commonly prescribed for treatment of Lambert-Eaton myasthenic syndrome
***TPMT* and *NUDT15* Variant Analysis**	***TPMT* and *NUDT15* Variant Analysis**
XXIII. *TMPT* and *NUDT15* variant analysis (81306, 81335, 0034U, 0169U) to determine drug metabolizer status may be 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 Azasa 2. Mercaptopurine[2] (e.g., Purinethol and Purixan) 3. Thioguanine[3] (e.g., Tabloid) B. The member is on thiopurine therapy and has had abnormal complete blood count results that do not respond to dose reduction.	XXIII. *TMPT* and *NUDT15* variant analysis (81306, 81335, 0034U, 0169U) to determine drug metabolizer status may be 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 Azasa 2. Mercaptopurine[2] (e.g., Purinethol and Purixan) 3. Thioguanine[3] (e.g., Tabloid) B. The member is on thiopurine therapy and has had abnormal complete blood count results that do not respond to dose reduction.
XXIV. *TPMT* and *NUDT15* variant analysis (81306, 81335, 0034U, 0169U) to determine drug metabolizer status is considered **investigational** for all other indications.	XXIV. *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	[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
***UGT1A1* Variant Analysis**	***UGT1A1* Variant Analysis**
XXV. *UGT1A1* variant analysis (81350) to determine drug metabolizer status may be considered **medically necessary** when:	XXV. *UGT1A1* variant analysis (81350) to determine drug metabolizer status may be considered **medically necessary** when:

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
A. The member is being considered for or is currently undergoing treatment with **any** of the following: 1. Irinotecan[1] (e.g., Onivyde, Camptosar) 2. Belinostat[2] (e.g., Beleodaq) 3. Sacituzumab govitecan-hziy[3] (e.g., Trodelvy).	A. The member is being considered for or is currently undergoing treatment with **any** of the following: 1. Irinotecan[1] (e.g., Onivyde, Camptosar) 2. Belinostat[2] (e.g., Beleodaq) 3. Sacituzumab govitecan-hziy[3] (e.g., Trodelvy).
XXVI. *UGT1A1* variant analysis (81350) to determine drug metabolizer status is considered **investigational** for all other indications.	XXVI. *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 cancers [2] Commonly prescribed for treatment of peripheral T-cell lymphoma [3] Commonly prescribed for treatment of breast and urothelial cancers	[1] Commonly prescribed for treatment of colon and rectal cancers [2] Commonly prescribed for treatment of peripheral T-cell lymphoma [3] Commonly prescribed for treatment of breast and urothelial cancers
***UGT2B17* Variant Analysis**	***UGT2B17* Variant Analysis**
XXVII. *UGT2B17* variant analysis (81479) to determine drug metabolizer status may be **medically necessary** when: A. The member is being considered for or is currently undergoing treatment with belzutifan[1] (e.g., Welireg).	XXVII. *UGT2B17* variant analysis (81479) to determine drug metabolizer status may be **medically necessary** when: A. The member is being considered for or is currently undergoing treatment with belzutifan[1] (e.g., Welireg).
XVIII. *UGT2B17* variant analysis (81479) to determine drug metabolizer status is considered **investigational** for all other indications.	XVIII. *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	[1] Commonly prescribed to treat tumors in individuals with Von Hippel-Lindau syndrome
***VKORC1* Variant Analysis**	***VKORC1* Variant Analysis**
XXIX. *VKORC1* variant analysis (81355) to determine drug metabolizer status may be considered **medically necessary** when: A. The member is being considered for or is currently undergoing treatment with warfarin[1] (e.g., Coumadin, Jantoven).	XXIX. *VKORC1* variant analysis (81355) to determine drug metabolizer status may be considered **medically necessary** when: A. The member is being considered for or is currently undergoing treatment with warfarin[1] (e.g., Coumadin, Jantoven).
XXX. *VKORC1* variant analysis (81355) to determine drug metabolizer status is considered **investigational** for all other indications.	XXX. *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	[1] Commonly prescribed to reduce the formation of blood clots

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Warfarin Sensitivity Analysis Panels XXXI. Multigene panel analysis to determine drug metabolizer status for warfarin[1] sensitivity (81227, 81355, 0030U) may be considered **medically necessary** when: A. The member is undergoing prophylaxis and treatment of venous thrombosis or pulmonary embolism, **OR** B. The member is undergoing prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, **OR** C. The member has a history of previous myocardial infarction, **AND** D. The member is being considered for or is undergoing treatment with warfarin, **AND** 1. The member has not reached a therapeutic dose. XXXII. 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 **Other Single Gene Variant Analysis** XXIII. 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. *SLCO1B1* (81328) F. *TYMS* (81479)	**Warfarin Sensitivity Analysis Panels** XXXI. Multigene panel analysis to determine drug metabolizer status for warfarin[1] sensitivity (81227, 81355, 0030U) may be considered **medically necessary** when: A. The member is undergoing prophylaxis and treatment of venous thrombosis or pulmonary embolism, **OR** B. The member is undergoing prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, **OR** C. The member has a history of previous myocardial infarction, **AND** D. The member is being considered for or is undergoing treatment with warfarin, **AND** 1. The member has not reached a therapeutic dose. XXXII. 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 **Other Single Gene Variant Analysis** XXIII. 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. *SLCO1B1* (81328) F. *TYMS* (81479)