

MEDICAL POLICY	Genetic Testing: Pharmacogenetic Testing (Medicare Only)	
Effective Date: 01/01/2021  <div style="text-align: right;">1/1/2021</div>	Section: GT	Policy No: 423
	Medical Policy Committee Approved Date: 8/18; 12/18; 3/19; 6/19; 9/19; 11/19; 07/2020; 12/2020	
Medical Officer	Date	

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

Medicare only

POLICY CRITERIA

Notes:

- This policy does not address genetic tests to determine drug therapy for the following indications:
 - TPMT testing for inflammatory bowel disease.
 - Non-small cell lung cancer targeted therapies (e.g., EGFR, ALK, ROS1, RET genes).
 - BCR-ABL1 fusion gene testing, which may be considered medically necessary.
 Please see [Medical Policy Cross References](#) section below for medical policies that may apply to these pharmacogenetic tests.
- This policy does not address multigene pharmacogenetic panel tests for selecting medications or doses of medication, which are considered **investigational and not covered**. Please see the PHP *Genetic Testing: Non-covered Genetic Panel Tests (Medicare Only)* Medical Policy for examples of pharmacogenetic panel tests which are considered investigational. This includes but is not limited to panels that include more than one CYP450 gene and panels for evaluating drug-metabolizer status.
- Please refer to the Providence Health Plan Pharmacy Coverage Policies (See [Medical Policy Cross References](#) section below) for information regarding targeted therapies associated with genetic testing addressed in this policy.

Policy Criteria Links

- Medically Necessary Genetic Tests
- Not Medically Necessary Genetic Tests:
 - [Statutorily Excluded Genes](#)
 - [Nationally Non-Covered Indications](#)
- [Tests based on PHP commercial medical policy criteria](#)

This policy is based on several Centers for Medicare & Medicaid Services (CMS) Local Coverage Determination (LCDs) and Local Coverage Articles (LCAs). This CMS guidance was identified as of the last policy review date on 2/13/2019.

Nationally Covered Indications (see [Policy Guidelines](#) section below)¹

- I. Next Generation Sequencing (NGS) tests may be considered **medically necessary and covered**, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when **both of the following** requirements are met (A. and B.):
 - A. Patient meets **all** of the following (1. – 3.):
 1. Either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; **and**
 2. Either not been previously tested using the same NGS test for the same primary diagnosis of cancer, or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; **and**
 3. Decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
 - B. The diagnostic laboratory test using NGS must meet **all** of the following (1. – 3.):
 1. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; **and**
 2. An FDA-approved or -cleared indication for use in that patient's cancer; **and**
 3. Results provided to the treating physician for management of the patient using a report template to specify treatment options.
- II. NGS tests for patients with cancer is considered **not medically necessary and not covered** if the cancer patient does not meet the criterion I.A. above.

BRACAnalysis CDx® Test^{2,3}

- III. The BRACAnalysis CDx may be considered **medically necessary and covered** to detect mutated BRCA genes in women when **all** of the following are met (A. – C.):
 - A. There is a diagnosis of ovarian or breast cancer; **and**

- B. They have not been previously tested for BRCA mutations (see Policy Guidelines section below); **and**
- C. The results of the test are used as an aid in identifying patients with deleterious or suspected deleterious germline BRCA variants, who are or may become eligible for treatment with Lynparza® (olaparib).

CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing⁴⁻⁸

CYP2C19 Genetic Testing

- IV. CYP2C19 gene testing may be considered **medically necessary and covered** for patients with acute coronary syndrome (ACS) undergoing percutaneous coronary interventions (PCI) who are initiating or reinitiating Clopidogrel (Plavix) therapy.
- V. CYP2C19 gene testing is considered **investigational and not covered** when the above criterion is not met, including but not limited to:
 - A. Medical management of other indications, including but not limited to:
 1. ACS without PCI
 2. Stroke
 3. Peripheral artery disease
 - B. Use of the following medications, including but not limited to:
 1. Amitriptyline
 2. Clopidogrel for indications other than above
 3. Proton pump inhibitors
 4. Selective serotonin reuptake inhibitors
 5. Warfarin

CYP2D6 Genetic Testing

- VI. CYP2D6 gene testing may be considered **medically necessary and covered** to guide medical treatment and/or dosing for individuals for whom initial therapy is planned with either of the following (A. or B.):
 - A. Amitriptyline or nortriptyline for treatment of depressive disorders; **or**
 - B. Tetrabenazine doses greater than 50 mg/day, or re-initiation of therapy with doses greater than 50 mg/day.
- VII. CYP2D6 gene testing is considered **investigational and not covered** for the following medications, including but not limited to:
 - A. Antidepressants other than those listed above
 - B. Antipsychotics

- C. Codeine
- D. Donepezil
- E. Galantamine
- F. Tamoxifen

CYP2C9 and VKORC1 Genetic Testing

VIII. CYP2C9 or VKORC1 gene testing may be considered **medically necessary and covered** to predict warfarin responsiveness when the patient has met **all** of the following (A. – C.):

- A. Have not been previously tested for CYP2C9 or VKORC1 alleles; **and**
- B. Have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; **and**
- C. Are enrolled in a prospective, randomized, controlled clinical study when that study meets the standards as set forth in [National Coverage Determination 90.1](#).

IX. CYP2C9 or VKORC1 gene testing is considered **not medically necessary and not covered** when the above criterion is not met.

X. CYP2C9 or VKORC1 gene testing is considered **investigational and not covered** for all other medications, including but not limited to:

- A. Celecoxib
- B. Fluoribiprofen
- C. Flovoxamine
- D. Siponimod

GeneSight® Psychotropic Pharmacogenetic Panel Test^{9,10}

XI. The GeneSight® Psychotropic pharmacogenetic panel test may be considered **medically necessary and covered** when **both** of the following are met (A. and B.):

- A. The provider is a licensed psychiatrist or neuropsychiatrist contemplating an alteration in neuropsychiatric medication; **and**
- B. The patient meets both of the following (1. and 2.):
 1. Has been diagnosed with major depressive disorder (MDD) (in accordance with the [Diagnostic and Statistical Manual of Mental Disorders](#) [DSM] IV/V criteria); **and**
 2. Is suffering from refractory moderate to severe depression (based upon DSM-V criteria) after at least one prior neuropsychiatric medication failure.

FDA-Approved Tests¹¹⁻¹⁶BRAF

- XII. Two tests have met the FDA criteria for BRAF genetic testing and may be considered **medically necessary and covered** for targeted therapy for melanoma when the following criteria are met (A.-B.):
- A. The **cobas[®] 4800 BRAF V600 test** to detect the presence of a mutation in the BRAF gene in melanoma cells and determine if a patient is eligible for Zelboraf[™](vemurafenib), a treatment indicated for a melanoma that cannot be surgically excised or has spread in the body.
 - B. The **ThxID[™] BRAF V600E/K test** to detect the BRAF mutations in selecting melanoma patients whose tumors carry the following BRAF mutations:
 - 1. V600E for treatment with dabrafenib [Tafinlar[®]]
 - 2. V600E or V600K mutation for treatment with trametinib [Mekinist[™]]

KRAS

- XIII. Two tests have met the FDA criteria for KRAS genetic testing and may be considered **medically necessary and covered** for targeted therapy for colorectal cancer (CRC) in the following situations:
- A. The **therascreen[®] KRAS test** to detect seven somatic mutations in the human KRAS oncogene was developed to aid in the identification of CRC patients for treatment with Erbitux[®] (cetuximab).
 - B. The **cobas[®] KRAS test** to detect mutations in codons 12 and 13 of the KRAS gene was developed to aid in identification of CRC patients for treatment with Erbitux[®] (cetuximab) or Vectibix[®] (panitumumab).

IDH2

- XIV. The **Abbott RealTime IDH2 test** has met the FDA criteria for IDH2 genetic testing and may be considered **medically necessary and covered** for targeted therapy for acute myeloid leukemia (AML) when the following criteria are met:
- A. The patient is an adult with relapsed or refractory AML; **and**
 - B. The test is to determine treatment with enasidenib (IDHIFA[®]).

HLA -B*15:02 Genotyping^{17,18}

- XV. HLA-B*15:02 genotype testing may be considered **medically necessary and covered** when both of the following are met:

- D. Patient is of Asian and Oceanian ancestry; **and**
- E. Initial treatment with carbamazepine, phenytoin or fosphenytoin is planned.

Statutorily Excluded Genes

XVI. Testing of the following genes, whether as single gene test or as part of a multi-gene panel test, for any indication, is considered **not medically necessary and not covered**:¹⁹⁻²⁹

- A. CFTR
- B. CYP2B6
- C. KIF6
- D. MMACHC
- E. UGT1A1
- F. VEGFR2

SULT4A1 Gene Testing^{30,31}

XVII. SULT4A1 gene testing, whether as single gene test or as part of a multi-gene pharmacogenetic panel test, is considered **not medically necessary and not covered** for determining medical management, including but not limited to predicting response to antipsychotic drug therapy.

SLC6A4 (also known as HTTLPR) Gene Testing³²

XVIII. SLC6A4 (also known as HTTLPR) gene testing is considered **not medically necessary and not covered** for determining response to selective serotonin reuptake inhibitors.

SLCO1B1 Gene Testing^{33,34}

XIX. SLCO1B1 gene testing is considered **not medically necessary and not covered** for assessing the effectiveness of statin therapy.

Not Medically Necessary Tests^{35,36}

XX. Genetic testing of the MTHFR gene for all risk factors, signs, symptoms, diseases, or conditions, including cardiovascular risk assessment, is **not medically necessary and is not covered**.

Nationally Non-Covered Indications (see Policy Guidelines section below)³⁷

XXI. Population screening, including genetic testing of asymptomatic individuals for pharmacogenetic indications is considered **not medically necessary and is not covered**. Such testing is considered screening and is excluded by Medicare statute.

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The Providence Health Plan (PHP) CMS Medical Policy Manual (UM382) hierarchy of coverage indicates that in the absence of an NCD, LCD, LCA, or other coverage guideline, CMS allows coverage determinations to be based on an objective, evidenced-based process. Therefore, the PHP commercial medical policy criteria have been applied to some of the panel tests listed, in the absence of Medicare coverage guidance:

Medically Necessary Pharmacogenetic Tests

XXII. The following pharmacogenetic tests may be considered **medically necessary and covered** when the testing of the gene(s) in column I. is performed based on suspicion or diagnosis of the condition in column II. when the drug(s) in column III. is being considered. (see table below)

Please see the Policy Guideline section for specific FDA and practice guideline use indications.

Hereditary Non-oncologic Conditions		
Column I Gene Test(s)	Column II Condition(s)	Column III Drug(s)
APOB, LDLR, LDLRAP1 and/or PCSK9	Familial Hyper-cholesterolemia	PRALUENT® (alirocumab)
APOB, LDLR, LDLRAP1 and/or PCSK9	Familial Hyper-cholesterolemia	REPATHA (evolocumab)
APOB, LDLR, LDLRAP1 and/or PCSK9	Familial Hyper-cholesterolemia	<ul style="list-style-type: none"> • KYNAMRO (mipomersen) • JUXTAPID® (lomitapide)
APOB, LDLR, LDLRAP1 and/or PCSK9	Familial Hyper-cholesterolemia	ZETIA® (ezetimibe)
CYP27A1	Cerebrotendinous xanthomatosis	Chenodal (chenodiol)
Factor 12 (FXII)	Hereditary angioedema (HAE) type III	Bradykinin B2 receptor antagonist: <ul style="list-style-type: none"> • Firazyr® (icatibant) C1 Esterase Inhibitors: <ul style="list-style-type: none"> • Berinert® • Cinryze® • Haegarda® • Ruconest® Kallikrein inhibitor: <ul style="list-style-type: none"> • Kalbitor® (ecallantide)
NLRP3	Cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome	Arcalyst™ (riloncept)

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	(FCAS) and Muckle-Wells syndrome (MWS)	
SMN1	Spinal muscular atrophy (SMA)	Spinraza® (nusinersen)
TPP1	Neuronal ceroid lipofuscinosis type 2 (CLN2), late infantile	Brineura® (cerliponase alfa)
Oncologic Indications		
Column I Gene Test(s)	Column II Condition(s)	Column III Drug(s)
BCR-ABL1 kinase domain mutations	acute lymphoblastic leukemia (ALL)	<p><i>Tyrosine kinase inhibitors:</i></p> <ul style="list-style-type: none"> • Tasigna® (nilotinib) (mutations: V299L , T315A, F317L, F317V, F317I, F317C) • Bosulif® (bosutinib) (mutations: Y253H, E255K, E255V, T315A, F317L, F317V, F317I, F317C F359V, F359C, F359I) • Iclusig® (ponatinib) (mutation: T315A) • Sprycel® (dasatinib) (mutations: Y253H, E255K, E255V, F359V, F359C, F359I) <p><i>Protein Synthesis Inhibitor:</i></p> <ul style="list-style-type: none"> • Synribo® (omacetaxine mepesuccinate) (mutation: T315A)
BCR-ABL1 kinase domain mutations	Chronic myeloid leukemia (CML)	<p><i>Tyrosine kinase inhibitors:</i></p> <ul style="list-style-type: none"> • Tasigna® (nilotinib) (mutations: V299L , T315A, F317L, F317V, F317I, F317C,) • Bosulif® (bosutinib) (mutations: Y253H, E255K, E255V, T315A, F317L, F317V, F317I, F317C F359V, F359C, F359I) • Iclusig® (ponatinib) (mutation: T315A) • Sprycel® (dasatinib) (mutations: Y253H, E255K, E255V, F359V, F359C, F359I) <p><i>Protein Synthesis Inhibitor:</i></p> <ul style="list-style-type: none"> • Synribo® (omacetaxine mepesuccinate) (mutation: T315A)
BRAF V600 mutation	Colon or rectal cancer	Zelboraf® (vemurafenib)
BRAF V600E mutation	Hairy-cell leukemia (HCL)	Zelboraf® (vemurafenib)
BRAF V600 mutations (confirmed in tumor specimen)	Melanoma (cutaneous)	Cotellic® (cobimetinib)
BRCA1/2	Breast Cancer	Talzenna™ (talazoparib)
BRCA1/2	Ovarian, fallopian tube, or primary peritoneal cancer	Rubraca® (rucaparib)

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Chromosome 17p deletion (del17p)	B-cell chronic lymphocytic leukemia (CLL)	Venclexta® (venetoclax)
FLT3	Acute myeloid leukemia (AML)	Xospata® (gilteritinib)
FLT3	Acute myeloid leukemia (AML)	Rydapt® (midostaurin)
IDH2	Acute myeloid leukemia (AML)	Tibsovo® (ivosidenib)
KIT D816V Mutation	Aggressive Systemic Mastocytosis (ASM)	Gleevec® (imatinib mesylate)
KRAS / NRAS	Colon or rectal cancer	<ul style="list-style-type: none"> • Erbitux® (cetuximab) • Vectibix® (panitumumab)
PDGFRB	Chronic myelomonocytic leukemia (CMML)	Gleevec® (imatinib mesylate)
PIK3CA	Metastatic breast cancer	PIQRAY® (alpelisib)

- XXIII. Pharmacogenetic testing is considered **investigational and is not covered** when criteria I. – XIII., or XXI. above is not met, including, but not limited to any of the following:
- A. Hereditary non-oncologic indications not listed above, including but not limited to:
 1. DMD gene testing to inform treatment with EXONDYS 51™ (eteplirsen)
 - B. Oncologic indications not listed above, including but not limited to:
 1. DPYD to guide 5-fluorouracil (5-FU) dosing and/or treatment
 2. TYMS to guide 5-fluorouracil (5-FU) dosing and/or treatment
 - C. Cytochrome P450 gene testing not addressed above, including but not limited to:
 1. CYP3A4
 2. CYP3A5

POLICY GUIDELINES

Molecular Diagnostic Services (MoIDX) Program

The Oregon Medicare contractor (MAC) has adopted the Molecular Diagnostic Services (MoIDX) program guidelines for their service area.”

According to the Noridian website regarding the MoIDX Program:³⁸

- “The MoIDX Program was developed by Palmetto GBA in 2011 to identify and establish coverage and reimbursement for molecular diagnostic tests. This program performs the following functions:
- Facilitates detailed and unique identification through registration of molecular diagnostic tests to facilitate claims processing and to track utilization.
 - Establishes clinical utility expectations.
 - Completes technical assessments of published test data to determine clinical utility and coverage.

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- Establishes reimbursement.

The MoIDX Program has determined certain gene tests do not meet Medicare’s medical necessary requirements and have therefore been deemed as statutory exclusions. Inclusion of one or more of these genes in a genetic panel test for any indication will result in an entire panel to be denied.

Next Generation Sequencing (NGS) Tests

As of 2/12/2019, the following FDA-approved companion diagnostic tests would be covered as long as all of the medical necessity criteria (in criterion I.) were met:

NGS Test	Diagnostic Manufacturer	FDA-Approved Indication(s) and Therapies
BRACAnalysis CDx	Myriad Genetic Laboratories, Inc.	Breast Cancer <ul style="list-style-type: none"> • Lynparza (olaparib) • Talzenna (talazoparib) Ovarian Cancer <ul style="list-style-type: none"> • Lynparza (olaparib) • Rubraca (rucaparib)
FoundationOne CDx (F1CDx)	Foundation Medicine, Inc.	Melanoma <ul style="list-style-type: none"> • Tafinlar (dabrafenib) • Zelboraf (vemurafenib) • Mekinist (trametinib) or Cotellic (cobimetinib) in combination with Zelboraf (vemurafenib) Breast cancer <ul style="list-style-type: none"> • Herceptin (trastuzumab) • Perjeta (pertuzumab) • Kadcyla (ado-trastuzumab emtansine) Colorectal cancer <ul style="list-style-type: none"> • Erbitux (cetuximab) • Vectibix (panitumumab) Ovarian cancer <ul style="list-style-type: none"> • Rubraca (rucaparib)
Praxis Extended RAS Panel	Illumina, Inc.	Colorectal cancer <ul style="list-style-type: none"> • Vectibix (panitumumab)

Please see the FDA website “[List of Cleared or Approved Companion Diagnostic Devices](#)” for the most current information on these tests and new tests as they are approved.³⁹

BRACAnalysis CDx®

BRACAnalysis CDx™ detects the presence of BRCA1 and BRCA2 gene mutations.

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Only one BRCA testing per beneficiary lifetime will be considered reasonable and necessary. If a patient received BRCA testing prior to Lynparza treatment consideration, regardless of the performing lab, additional testing would not be considered a reasonable and necessary service.

CMS Guidance on Genetic Screening Tests

According to the Medicare Claims Processing Manual, Chapter 16:³⁷

“Tests that are performed in the absence of signs, symptoms, complaints, personal history of disease, or injury are **not covered** except when there is a statutory provision that explicitly covers tests for screening as described.

If a person is tested to rule out or to confirm a suspected diagnosis because the patient has a sign and/or symptoms, this is considered a diagnostic test, not a screening test. A/B MACs (A) and (B) have discretionary authority to make reasonable and necessary scope of benefit determinations.”

Statutorily Excluded Tests

Benefits not addressed in Title XVIII of the Social Security Act (i.e. the Act) are known as being “statutorily excluded,” meaning, Medicare is not authorized to pay for them under the Act. Section Sec. 1862 (1)(A) of the act indicated that statutorily excluded services are deemed “not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member”.⁴⁰

For Criterion XXII: FDA and Practice Guideline Use Indications

Hereditary Non-oncologic Conditions	
Gene Test(s) Condition(s) & Drug(s)	FDA Indications/Usage and Clinical Practice Guidelines
APOB, LDLR, LDLRAP1 and/or PCSK9 Familial Hyper-cholesterolemia • PRALUENT® (alirocumab)	FDA Indications: As adjunct to maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia who require additional lowering of LDL-cholesterol (LDL-C)
APOB, LDLR, LDLRAP1 and/or PCSK9 Familial Hyper-cholesterolemia • REPATHA (evolocumab)	FDA Indications: -As an adjunct to diet, alone or in combination with other lipid-lowering therapies, for treatment of adults with heterozygous familial hypercholesterolemia to reduce LDL-C -As an adjunct to other LDL-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
APOB, LDLR, LDLRAP1 and/or PCSK9 Familial Hyper-cholesterolemia • KYNAMRO (mipomersen)	FDA Indications: To reduce LDL-C, apolipoprotein B (apo B), total cholesterol (T C), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with HoFH

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<ul style="list-style-type: none"> • JUXTAPID® (lomitapide) 	
APOB, LDLR, LDLRAP1 and/or PCSK9 Familial Hyper-cholesterolemia <ul style="list-style-type: none"> • ZETIA® (ezetimibe) 	<u>FDA Indications:</u> Reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), in combination with atorvastatin or simvastatin
CYP27A1 Cerebrotendinous xanthomatosis <ul style="list-style-type: none"> • Chenodal (chenodiol) 	<u>FDA Indications:</u> Designated as an orphan drug by the FDA. <u>PHP Pharmacy</u> Chenodal policy allows for off-label use of this drug to treat this rare condition.
Factor 12 (FXII) Hereditary angioedema (HAE) type III <ul style="list-style-type: none"> • Bradykinin B2 receptor antagonist: <ul style="list-style-type: none"> ○ Firazyr® (icatibant) ○ C1 Esterase Inhibitors: <ul style="list-style-type: none"> ○ Berinert® ○ Cinryze® ○ Haegarda® ○ Ruconest® • Kallikrein inhibitor: <ul style="list-style-type: none"> ○ Kalbitor® (ecallantide) 	<u>FDA Indications:</u> Indications for use differ by medication. Please refer to the FDA website.
NLRP3 Cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) <ul style="list-style-type: none"> • Arcalyst™ (rilonacept) 	<u>FDA Indications:</u> For adults and children 12 and older
SMN1 Spinal muscular atrophy (SMA) <ul style="list-style-type: none"> • Spinraza® (nusinersen) 	<u>FDA Indications:</u> For pediatric and adult patients
TPP1 Neuronal ceroid lipofuscinosis type 2 (CLN2), late infantile <ul style="list-style-type: none"> • Brineura® (cerliponase alfa) 	<u>FDA Indications:</u> For symptomatic pediatric patients 3 years of age and older

Oncologic Indications

Gene(s) Condition(s) & Drug(s)	FDA Indications/Usage and Clinical Practice Guidelines
BCR-ABL1 kinase domain mutations acute lymphoblastic leukemia (ALL) <ul style="list-style-type: none"> • Tyrosine kinase inhibitors <ul style="list-style-type: none"> ○ Tasigna® (nilotinib) (mutations: V299L, T315A, F317L, F317V, F317I, F317C,) ○ Bosulif® (bosutinib) (mutations: Y253H, E255K, E255V, T315A, F317L, F317V, F317I, F317C F359V, F359C, F359I) ○ Iclusig® (ponatinib) (mutation: T315A) 	<u>FDA Indications:</u> These FDA approved drugs are not approved for this indication but are recommended by NCCN. <u>Guidelines:</u> For therapy selection for relapsed or refractory ALL (Category 2A). ⁴¹

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<ul style="list-style-type: none"> ○ Sprycel® (dasatinib) (mutations: Y253H, E255K, E255V, F359V, F359C, F359I) • Protein Synthesis Inhibitor: <ul style="list-style-type: none"> ○ Synribo® (omacetaxine mepesuccinate) (mutation: T315A) 	
<p>BCR-ABL1 kinase domain mutations chronic myeloid leukemia (CML)</p> <ul style="list-style-type: none"> • Tassigna® (nilotinib) (mutations: V299L, T315A, F317L, F317V, F317I, F317C,) • Bosulif® (bosutinib) (mutations: Y253H, E255K, E255V, T315A, F317L, F317V, F317I, F317C F359V, F359C, F359I) • Iclusig® (ponatinib) (mutation: T315A) • Sprycel® (dasatinib) (mutations: Y253H, E255K, E255V, F359V, F359C, F359I) • Protein Synthesis Inhibitor: <ul style="list-style-type: none"> ○ Synribo® (omacetaxine mepesuccinate) (mutation: T315A) 	<p><u>FDA Indications:</u> Synribo®</p> <ul style="list-style-type: none"> • For adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI). <p>Iclusig®</p> <ul style="list-style-type: none"> • For adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase). <p><u>Guidelines:</u></p> <ul style="list-style-type: none"> • For therapy selection for chronic phase (Category 1) and disease progression to advanced phase CML (accelerated or blast) (Category 2A).⁴²
<p>BRAF V600 mutation Colon or rectal cancer</p> <ul style="list-style-type: none"> • Zelboraf® (vemurafenib) 	<p><u>FDA Indications:</u> This drug is not FDA- approved for this indication, but is recommended by NCCN.</p> <p><u>Guidelines:</u></p> <ul style="list-style-type: none"> • NCCN states that all patients with metastatic cancer should have tumor tissue genotyped for BRAF.^{8,43} • A primary treatment option for BRAF V600E-positive patients with unresectable metachronous metastases who have had previous adjuvant therapy. (Category 2A) • A subsequent therapy option for advanced or metastatic disease for BRAF V600E-positive patients who have had previous systemic therapy. <p>For both indications, to be used in combination with irinotecan and either Erbitux® or Vectibix®</p>
<p>BRAF V600E Hairy-cell leukemia (HCL)</p> <ul style="list-style-type: none"> • Zelboraf® (vemurafenib) 	<p><u>FDA Indications:</u> Zelboraf®</p> <ul style="list-style-type: none"> • This drug is not FDA- approved for this indication, but is recommended by NCCN. <p><u>Guidelines:</u></p> <ul style="list-style-type: none"> • NCCN states that BRAF V600E mutation testing is essential for HCL.⁴⁵ <p>One treatment option for progression after relapse or refractory therapy. (Category 2A)</p>
<p>BRAF V600 mutations (confirmed in tumor specimen) Melanoma (cutaneous)</p>	<p><u>FDA Indications:</u> COTELLIC® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.</p>

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<ul style="list-style-type: none"> • Cotellic® (cobimetinib) 	<p>There are two FDA-approved companion diagnostic tests, using formalin-fixed paraffin embedded (FFPE) tumor tissue specimens to detect V600E or V600E/V600K mutations.</p> <p><u>Guidelines:</u> NCCN states that cobimetinib may be used in combination with vemurafenib as first-line or second-line therapy for metastatic or unresectable disease.⁴⁶</p>
<p>BRCA1/2 Breast Cancer</p> <ul style="list-style-type: none"> • Talzenna™ (talazoparib) 	<p><u>FDA Indications:</u></p> <ul style="list-style-type: none"> • For adult patients with deleterious or suspected deleterious germline BRCA mutations HER2-negative locally advanced or metastatic breast cancer. • There is an FDA-approved companion diagnostic test, using whole blood specimens. <p><u>Guidelines:</u> For recurrent or stage IV (M1) disease:</p> <ul style="list-style-type: none"> • For patients with HER2-negative tumors and a germline BRCA mutation. (Category 1)⁴⁷ <p>Note: NCCN states that all patients with HER2 negative disease eligible for single-agent therapy strongly consider BRCA1/2 testing.</p>
<p>BRCA1/2 Ovarian, fallopian tube, or primary peritoneal cancer</p> <ul style="list-style-type: none"> • Rubraca® (rucaparib) 	<p><u>FDA Indications:</u> Epithelial ovarian, fallopian tube or primary peritoneal cancer:</p> <ul style="list-style-type: none"> • For the maintenance treatment of adult patients with recurrent cancer who are in a complete or partial response to chemotherapy • For the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated cancer who have been treated with two or more chemotherapies • There are two FDA-approved companion diagnostic tests available: <ul style="list-style-type: none"> ○ FoundationOne CDx™ requires FFPE tumor tissue (somatic mutations) ○ BRACAnalysis CDx uses whole blood specimens collected in EDTA (germline mutations) <p><u>Guidelines:</u> Epithelial ovarian, fallopian tube or primary peritoneal cancer:⁴⁸</p> <ul style="list-style-type: none"> • For maintenance treatment of adult patients with persistent or recurrent disease (Category 2A) Ovarian cancer • Same as FDA-approved language (Category 2A) <p>*Regardless of cancer, this agent is only recommended as single-agent therapy (Category 2A)</p>
<p>Chromosome 17p deletion (del17p) B-cell chronic lymphocytic leukemia (CLL)</p> <ul style="list-style-type: none"> • Venclexta® (venetoclax) 	<p><u>FDA Indications:</u></p> <ul style="list-style-type: none"> • For CLL patients with a 17p deletion who have received at least one prior therapy. • The companion diagnostic test is for detecting deletion of the LSI TP53 probe target (17p-) for treatment with VENCLEXTA®. • This test is not intended for monitoring of residual disease. <p><u>Guidelines:</u></p>

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	<ul style="list-style-type: none"> NCCN states that del17p status testing is useful during diagnostic work-up and must be re-evaluated prior to initial therapy for CLL and small lymphocytic lymphoma and for relapsed/refractory disease. (Category 2A)⁴⁹ Venclexta® for relapsed / refractory therapy, regardless of del(17p) status.
FLT3 Acute myeloid leukemia (AML) Xospata® (gilteritinib)	FDA Indications: For the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test.
FLT3 Acute myeloid leukemia (AML) Rydapt® (midostaurin)	FDA Indications: <ul style="list-style-type: none"> For newly diagnosed AML that is FLT3 mutation-positive. There is an FDA companion test to detect internal tandem duplication (ITD) mutations and the tyrosine kinase domain mutations D835 and I836 in the FLT3 gene, requiring peripheral blood or bone marrow aspirates.
IDH2 Acute myeloid leukemia (AML) Tibsovo® (ivosidenib)	FDA Indications: <ul style="list-style-type: none"> For the treatment of adult patients with relapsed or refractory AML with an IDH2 mutation.⁵⁰ Has a companion diagnostic test for five IDH1 R132 mutations (R132C, R132H, R132G, R132S, and R132L) in DNA extracted from human blood (EDTA) or bone marrow (EDTA).
KRAS / NRAS Colon or rectal cancer <ul style="list-style-type: none"> Erbitux® (cetuximab) Vectibix® (panitumumab) 	FDA Indications: Erbitux® <ul style="list-style-type: none"> For patients with KRAS wild-type, EGFR-expressing, metastatic colorectal cancer. Not indicated for treatment of Ras-mutant (KRAS and NRAS) colorectal cancer. Vectibix® (panitumumab) <ul style="list-style-type: none"> For the treatment of wild-type RAS (wild-type in both KRAS and NRAS) metastatic colorectal cancer (mCRC). Not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown. Note: There are several FDA-approved companion diagnostic tests for KRAS and KRAS/NRAS, requiring formalin-fixed paraffin embedded (FFPE) tumor tissue. Guidelines: <ul style="list-style-type: none"> NCCN states that all patients with metastatic cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) mutations.⁴³ A primary treatment option for BRAF V600E-positive patients with unresectable metachronous metastases who have had previous adjuvant FOLFOX/CAPEOX within the past 12 months. (Category 2A) A subsequent therapy option for advanced or metastatic disease for BRAF V600E-positive patients who have had previous oxaliplatin, irinotecan, FOLFOXIRI or fluoropyrimidine therapy. For both drugs, to be used in combination with irinotecan and Zelboraf®.
KIT D816V Mutation Aggressive Systemic Mastocytosis (ASM) Gleevec® (imatinib mesylate)	FDA Indications: <ul style="list-style-type: none"> The FDA companion diagnostic test requires fresh bone marrow samples.

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<p>PDGFRβ chronic myelomonocytic leukemia (CMML)</p> <ul style="list-style-type: none"> Gleevec® (imatinib mesylate) 	<p><u>FDA Indications:</u></p> <ul style="list-style-type: none"> The FDA companion diagnostic test says it is indicated for Myelodysplastic Syndrome / Myeloproliferative Disease (MDS/MPD). The test requires fresh bone marrow samples. <p><u>Guidelines:</u></p> <ul style="list-style-type: none"> NCCN states that patients with CMML should be evaluated for PDGFRβ gene arrangements as they may respond well to inhibitors like imatinib mesylate.⁵¹
<p>PIK3CA Advanced or metastatic breast cancer. PIQRAY® (alpelisib)</p>	<p><u>FDA Indications:</u></p> <ul style="list-style-type: none"> The FDA companion diagnostic test says it is indicated for breast cancer. Samples may be obtained from tissue and plasma. Testing may be useful the time a patient is diagnosed with advanced HR+/HER2-breast cancer, or when a HR+/HER2- patient presents with metastases from breast cancer. <p><u>Guidelines:</u></p> <p>NCCN recommended workup for recurrent or stage IV (M1) breast cancer includes assessing <i>PIK3CA</i> mutation status with tumor or liquid biopsy if HR-positive/HER2-negative and considering therapy with alpelisib. <i>PIK3CA</i> mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.⁴⁷</p>

BILLING GUIDELINES

Next Generation Sequencing Tests

Based on Transmittal #210, included in NCD 90.2, and the LCAs: A55224 and 55295, the following CPT codes are considered appropriate for billing for the FDA-approved companion diagnostic tests.¹⁻³

NGS Test	Code
BRACAnalysis CDx	81479 (3/16/18 - 12/31/18) 81162 (1/1/19 to present)
FoundationOne CDx (F1CDx)	81455(3/16/18 - 3/31/18) 0037U (4/1/18 to present)

Note: Although there is CMA guidance regarding the coverage of genetic testing of the KRAS and NRAS genes which make-up the FDA-approved Praxis Extended RAS Panel (LCAs A54500 and A55162), there is no guidance published by Medicare for this test.^{13,14} However, it may come in with one or more of the following CPT codes: 81275, 81276, 81311.

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CYP2C9 and/or VKORC1 Gene testing for Warfarin Response

Based on NCD 90.1 - Pharmacogenomic Testing for Warfarin Response,⁵ gene testing on CYP2C9 and/or VKORC1 will only be covered through coverage with evidence development (CED). Testing will be limited to once in a lifetime per patient. MoIDX will reimburse ONLY genetic testing services for beneficiaries who meet the medical policy criteria above AND are enrolled in a clinical trial.

For gene testing on CYP2C9 and/or VKORC1, report only G9143. Do NOT report 81227 (CYP2C9) and/or 81355 (VKORC1).

GeneSight® Psychotropic Test

GeneSight® testing may only be ordered by licensed psychiatrists or neuropsychiatrists. Provider may have primary boards in internal medicine or neurology and also have boards in psychiatry or neuropsychiatry and the provider has a designated specialty in PECOS as IM/neurology. Providers ordering the test must affix a KX modifier attesting that they have psychiatry or neuropsychiatry boards.

CPT/HCPCS CODES

Medicare Only	
Prior Authorization Required	
0028U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, copy number variants, common variants with reflex to targeted sequence analysis
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis, utilizing formalin-fixed paraffin-embedded tissue
0154U	FGFR3 (fibroblast growth factor receptor 3) gene analysis (ie, p.R248C [c.742C>T], p.S249C [c.746C>G], p.G370C [c.1108G>T], p.Y373C [c.1118A>G], FGFR3-TACC3v1, and FGFR3-TACC3v3)
0155U	PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) (eg, breast cancer) gene analysis (ie, p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y)
0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score
0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status

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0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *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) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)
81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)
81232	DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)
81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
81283	IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative

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81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)
81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81346	TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)

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81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)
No Prior Authorization Required	
0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin
0046U	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)

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81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81379	HLA Class I typing, high resolution (ie, alleles or allele groups); complete (ie, HLA-A, -B, and -C)
81380	HLA Class I typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-A, -B, or -C), each
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88272	Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)
88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
Not Covered	
0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (ie, *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) (eg, citalopram metabolism) gene analysis, common variants (ie, 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)(eg, thiopurine metabolism) gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81306	NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6)

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81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then prior-authorization is required.	
81479	Unlisted Molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
84999	Unlisted chemistry procedure

DESCRIPTION

Next Generation Sequencing (NGS) Tests

Clinical laboratory diagnostic tests can include tests that, for example, predict the risk associated with one or more genetic variations. In addition, in vitro companion diagnostic laboratory tests provide a report of test results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product. Next Generation Sequencing (NGS) is one technique that can measure one or more genetic variations as a laboratory diagnostic test, such as when used as a companion in vitro diagnostic test.

Patients with cancer can have recurrent, relapsed, refractory, metastatic, and/or advanced stages III or IV of cancer. Clinical studies show that genetic variations in a patient’s cancer can, in concert with clinical factors, predict how each individual responds to specific treatments.

In application, a report of results of a diagnostic laboratory test using NGS (i.e., information on the cancer’s genetic variations) can contribute to predicting a patient’s response to a given drug: good, bad, or none at all. Applications of NGS to predict a patient’s response to treatment occurs ideally prior to initiation of such treatment.

Pharmacogenomic Testing

Pharmacogenomics denotes the study of how an individual's genetic makeup, or genotype, affects the body's response to drugs. Pharmacogenomics as a science examines associations among variations in genes with individual responses to a drug or medication. In application, pharmacogenomic results (i.e., information on the patient’s genetic variations) can contribute to predicting a patient’s response to a given drug: good, bad, or none at all.

CYP2C19 Testing

The CYP450 gene superfamily is composed of many isoenzymes that are involved in the metabolism of about 75% of commonly prescribed drugs. CYP2C19 metabolizes 15% of all currently used drugs,

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whereas CYP2D6 enzymes metabolize approximately 20-25%, and CYP2C9 metabolizes approximately 10%.

Genetic alterations or “polymorphisms” are common in these isoenzymes, with more than 30 polymorphisms identified in CYP2C19. These polymorphisms can lead to differences in individual drug response secondary to variation in metabolism.

CYP2C19 phenotypes include poor, intermediate, extensive and ultra-rapid metabolizers. The frequency of the various metabolizers phenotypes has been estimated as follows:

- 2-15% - poor metabolizers
- 18-45% - intermediate metabolizers
- 35-50% - extensive metabolizers
- 5-30% - ultra-rapid metabolizers

The genotypic rates vary by ethnicity. Approximately 2% of whites, 4% of blacks and 14% of Chinese are poor CYP2C19 metabolizers.

Pharmacogenetic testing has been proposed to predict individual response to a variety of CYP2C19-metabolized drugs including clopidogrel, proton pump inhibitors, and tricyclic antidepressants, among others. In certain scenarios, an individual patient may benefit from genetic testing in determining dosage and likely response to specific medications.

Clopidogrel bisulfate (Plavix) is a widely prescribed medication to/for:

- Prevent blood clots in patients with acute coronary syndrome (ACS),
- Other cardiovascular (CV) disease-related events,
- Undergoing percutaneous coronary intervention

Clopidogrel response varies significantly due to genetic and acquired factors including obesity, smoking and non-compliance. Patients with poor response to clopidogrel may experience recurrent CV event or thrombotic events while taking clopidogrel. They are at greater risk for major adverse CV events such as heart attack, stroke and death. These individuals are typically poor to intermediate metabolizers of clopidogrel due to the presence of the associated CYP2C19 polymorphisms. These individuals should be given an alternate treatment strategy (Plavix PI).

CYP2D6 Testing

Genetic alterations or “polymorphisms” are common in these isoenzymes, with more than 100 polymorphisms identified in CYP2D6. These polymorphisms can lead to differences in individual drug response secondary to variation in metabolism.

CYP2D6 phenotypes include poor, intermediate, extensive and ultra-rapid metabolizers. The frequency of the poor metabolizer phenotype varies by ethnicity with 7-10% in Caucasians, 1.9-7.3% in African-

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Americans, and $\leq 1\%$ in most Asian populations studied. The extensive metabolizer phenotype, observed in 50% of Caucasians, is the most common in this population. Genetic variation, as well as drug-drug interactions, can influence the classification of CYP2D6 metabolism into one of the above phenotypes. In addition, chronic dosing of a CYP2D6 drug can inhibit its own metabolism over time as the concentration of the drug approaches a steady state.

Pharmacogenetic testing has been proposed to predict individual response to a variety of CYP2D6-metabolized drugs including tamoxifen, antidepressants, opioid analgesics, and tetrabenazine for chorea, among others. In certain scenarios, an individual patient may benefit from this genetic testing in determining dosage and likely response to specific medications.

CYP2C9 Testing

CYP2C9 metabolizes approximately 10-15% of all currently used drugs. Genetic alternations or “polymorphisms” are common in these isoenzymes, with 57 polymorphisms identified in CYP2C9, which can lead to differences in individual drug response secondary to variation in metabolism.

Pharmacogenetic testing has been proposed to predict individual response to a variety of CYP2C9-metabolized drugs including celecoxib, flurbiprofen, fluvoxamine and warfarin, among others. In certain scenarios, an individual patient may benefit from this genetic testing in determining dosage and likely response to specific medications.

Individuals with low enzyme activity for CYP2C9 substrates are at risk of adverse drug reactions. However, pharmacogenetic testing for individuals being treated with drugs, such as warfarin, may experience little or no benefit from testing. This is, in part, because the CYP2C9 genotype accounts for only part of the variability in drug sensitivity.

Pharmacogenomic Testing for Warfarin Response

Warfarin sodium is an orally administered anticoagulant drug that is marketed most commonly as Coumadin®. Warfarin affects the vitamin K-dependent clotting factors II, VII, IX, and X. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex, thereby reducing the regeneration of vitamin K1 epoxide. The elimination of warfarin is almost entirely by metabolic conversion to inactive metabolites by cytochrome P450 (CYP) enzymes in liver cells. CYP2C9 is the principal cytochrome P450 enzyme that modulates the anticoagulant activity of warfarin. From results of clinical studies, genetic variation in the CYP2C9 and/or VKORC1 genes can, in concert with clinical factors, predict how each individual responds to warfarin.

Pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict a patient’s response to warfarin occurs ideally prior to initiation of the drug. This would be an once-in-a-lifetime test, absent any reason to believe that the patient’s personal genetic characteristics would change over time. Although such pharmacogenomic testing would be used to attempt to better approximate the best starting dose of

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warfarin, it would not eliminate the need for periodic PT/INR testing, a standard diagnostic test for coagulation activity and for assessing how a patient is reacting to a warfarin dose.

VKORC1 Testing

The vitamin K epoxide reductase complex subunit 1, encoded by the gene VKORC1, is critical in the vitamin K pathway for coagulation. Warfarin therapy targets VKORC1 to reduce clotting risk.

Variation in response to warfarin therapy has been linked to genetic variations. Retrospective study of European-American patients undergoing long term warfarin therapy identified 5 major haplotypes that were most predictive of approximately 25% of variance in warfarin dose. These are classified into A: low dose haplotype and B: high dose haplotype. This was validated in two European-American populations. Average maintenance dose for A/A haplotypes was approximately 2.7 mg per day; 4.9 mg per day for A/B, and 6.2 mg per day for B/B (p<0.001).

GeneSight® Psychotropic Panel Test

GeneSight® Psychotropic is a multiplex pharmacogenomic test involving the analysis of fifty alleles (SNPs) from six different genes and a clinical outcomes-based decision support modeling tool that weights the influence of the various alleles/SNPs with respect to thirty-two different psychotropic pharmaceutical agents. The test results in the differentiation of psychoactive drugs that are likely to be effective and well-tolerated by a particular patient versus those that are not. In multiple prospective clinical studies, the use of GeneSight® to guide neuropsychiatric pharmaceutical selection and prescription has demonstrated an increased patient response to treatment from 60% to 250% (as measured by the standardized 17-item Hamilton Rating Scale for Depression or HAM-17; response is defined as ≥ 50% reduction in HAM-D17 score) versus unguided, empirical treatment (or treatment as usual).

GeneSight® has particular relevance for Medicare beneficiaries, 26% of whom experience a mental disorder each year. Additionally, six out of ten disabled Medicare beneficiaries (~3.7 million) under age 65, representing roughly 17% of all beneficiaries, have a diagnosis of mental disorder. Furthermore, the American Psychiatric Association (APA) recognizes depression as the most common mental disorder in people aged 65 and older. It frequently appears as a co-morbid symptom to other conditions and can even mimic the symptoms of dementia. As a group, seniors generally take more medications than other age groups, increasing their risk of drug-drug interactions and adverse drug events (ADEs).

The GeneSight® report segments and displays these psychotropic medications into three “traffic light” categories or “bins” - green, yellow and red. Based on the patient’s genetic make-up and the drug’s metabolic and therapeutic pathways, the green bin identifies drugs that will likely be well tolerated and efficacious for the tested patient; the yellow bin identifies drugs with an intermediate effect; and the red bin identifies drugs likely to be poorly tolerated and/or ineffective. The report also identifies common drug-drug interactions that are similarly influenced by the patient’s genetic composition.

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HLA-B*15:02 Genotype Testing

In 2004, researchers reported individuals with the HLA-B*1502 had an increased risk to develop Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) when exposed to carbamazepine. SJS and TEN, considered two variants of a disease continuum, are severe, sometimes lethal diseases of the skin and mucous membranes. A third, intermediate condition is called SJS/TEN. The most serious cases result in separation of the epidermis from the dermis in large sheets, which can also lead to infection. Sloughing can also occur in the bronchial, gastrointestinal and ocular epithelia.

Estimates indicate 10-15% of the population from China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan carry the HLA-B*1502 allele. South Asians, including Indians, appear to have an intermediate chance of having HLA-B*1502, averaging 2 to 4%, but it is higher in some subgroups. Oceanians also have an increased incidence of HLA-B *1502 serotype. The incidence of the HLA-B*1502 serotype in the European Caucasian population has been reported at less than 0.1%, in the African population as 0.2% and in the Native American and Hispanic populations as 0%.

In 2007, the FDA issued a black box label warning for carbamazepine stating, “Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment.” More recent evidence has supported the FDA recommendations and at least one study has demonstrated that prospective screening of HLA-B*1502 has reduced the incidence of SJS/TEN in a Chinese population.

REVIEW OF EVIDENCE

CYP2C19 Testing

The clinical utility of CYP2C19 genotyping has been supported with net benefits on improving health outcomes for individuals with ACS who are undergoing percutaneous coronary interventions (PCI). There is insufficient evidence of clinical utility of CYP2C19 genotyping for individuals considering clopidogrel therapy for other indications, such as medical management of ACS without PCI, stroke, or peripheral artery disease.

With regards to CYP2C19 testing for antidepressant treatment, recent evidence has suggested genetic testing prior to initiating certain tricyclic antidepressants, namely amitriptyline, due to the effects of the genotype on drug efficacy and safety. Use of this information to determine dosing has been proposed to improve clinical outcomes and reduce the failure rate of initial treatment. However, the Clinical Pharmacogenetics Implementation Consortium did not have enough evidence to make a strong recommendation for dose modification based on genotype, and a moderate recommendation was given based on data outside of randomized trials. Additionally, even with genotype information, a suggestion is given to start patients on low dose, gradually increasing to avoid adverse side effects. Consequently, genotyping is not needed with this approach.

Proton pump inhibitors are used to treat several gastric acid-related conditions including duodenal ulcer, gastric ulcer and gastroesophageal reflux disease. Proton pump inhibitors can also be used to

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treat *Helicobacter pylori*. Several proton pump inhibitors are metabolized by CYP2C19. However, there is insufficient data to warrant CYP2C19 genotyping to determine health outcomes or adverse drug reactions in treatment with proton pump inhibitors.

With regards to serotonin reuptake inhibitors, there is insufficient evidence to support CYP2C19 genotyping to determine medical management for the treatment of obsessive compulsive disorder at this time.

CYP2D6 Testing

Tamoxifen

Available evidence fails to support direct evidence of clinical utility for testing of CYP2D6 in treatment with tamoxifen. Tamoxifen metabolism and the causes for resistance are complex rather than the result of a single polymorphism.

Antidepressants

In regards to CYP2D6 testing for antidepressant treatment, there was insufficient evidence in the past to support testing to determine treatment. More recently, evidence has supported the use of genetic testing prior to initiating certain tricyclic antidepressants due to the effects of genotype on drug efficacy and safety. Use of this information to determine dosing can improve clinical outcomes and reduce the failure rate of initial treatment. However, there is insufficient evidence for CYP2D6 genotyping for individuals considering antipsychotic medications or other antidepressants with CYP2D6 as a metabolizing enzyme.

Codeine

In addition, the role of CYP2D6 genotyping has been evaluated for use in opioid analgesic drug therapy, specifically codeine analgesia. The efficacy and toxicity, including severe or life-threatening toxicity after normal doses of codeine has been linked to an individual's CYP2D6 genotype. However, genotyping would indicate avoidance of codeine due to risk of adverse events in only 1-2% of the populations, and there is considerable variation in the degree of severity of adverse events, with most not classified as serious. Furthermore, codeine is widely used without genotyping. At this time, there is insufficient evidence to support clinical utility of genotyping for management of codeine therapy.

Tetrabenazine

The dosing of tetrabenazine is based, in part, on CYP2D6 genotyping. However, a recent study suggests that the necessity to genotype may need to be reconsidered. The Xenazine® manufacturer package insert indicates that poor metabolizers of CYP2D6 should not exceed a maximum dose of 50 mg/day.

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Drugs for Alzheimer’s Disease

Galantamine is an antideementia drug used in the treatment of Alzheimer’s disease. Studies have been performed that reveal the CYP2D6 genotype significantly influences galantamine concentrations in blood. Still other studies have revealed that urinary assays for CYP2D6 phenotype are technically feasible. At this time, the association between phenotype and drug responsiveness remains unknown. It has been suggested that confirmation studies in larger populations are necessary to establish evidence regarding individuals most likely to benefit from galantamine, including information on treatment efficacy and tolerability.

Donepezil (Aricept) is a drugs used to treat an Alzheimer’s disease. Some studies have reported an influence of the CYP2D6 on the response to treatment with this drug. Other studies suggest that therapy based on CYP2D6 genotype is unlikely to be beneficial for treating Alzheimer’s disease patients in routine clinical practice. Additional studies are needed to determine the efficacy and utility of CYP2D6 genotyping in those patients who are treated with donepezil.

CYP2C9 Testing

Warfarin

While there is extensive literature regarding warfarin and the CYP2C9 genotype, the clinical utility of such testing remains unproven at this time. In fact, pharmacogenetic testing for warfarin treatment has been recommended against by the American College of Medical Genetics and the American College of Chest Physicians. These guidelines suggest that genetic testing for warfarin metabolism is not medically necessary, and evidence of clinical utility remains to be proven. Obstacles for determining clinical utility have been reviewed with suggestions for researchers in this area.

Celecoxib

In addition, limited information is available regarding celecoxib metabolism in individuals with CYP2C9 polymorphisms. More trials are needed to determine clinical utility and appropriateness of pharmacogenetic testing in this population.

VKORC1 Testing

Review by the American College of Medical Genetics (2008) confirmed the analytic validity of testing VKORC1 and confirmed that there is sufficient evidence to support association with final therapeutic dose of warfarin. However, safe warfarin dosing requires careful monitoring and there is insufficient evidence is available to support routine VKORC1 genotyping for determination of final dosing. Further study in prospective clinical trials are needed to determine clinical utility.

Clinical Pharmacogenetics Implementation Consortium guidelines recommend that pharmacogenetic algorithms be used to determine ideal dosing, and recommend including VKORC1 genotyping when available. However, the evidence from randomized prospective trials is limited, and impact on clinical

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outcomes is not yet known, limiting the ability to recommend that genotyping be performed for initial warfarin prescribing.

Prospective study of 30 healthy subjects assessed for warfarin dosing with daily INR measurements determined that VKORC1 (p=0.02) variant carriers require lower cumulative doses of warfarin to achieve INR \geq 2.0. Participants who carried variants in both CYP2C9 and VKORC1 required fewer days to achieve INR \geq 2.0 than wild type subjects (p=0.01) resulting in an estimated genetic contribution to dose variability of 62%.

Meta-analysis of CYP2C9 and VKORC1 genotypes influence the risk of hemorrhagic complications in warfarin treated patients and increase the risk for over-coagulation and hemorrhagic complications with CYP2C9*3 carriers. No significant association was noted between VKORC1 genotypes and hemorrhagic complications.

Randomized controlled study assessing 109 adult patients and the influence of VKORC1 genotyping data on clinical outcomes of initial warfarin dosing was performed. Primary endpoints included time in therapeutic range over 90 days and number of anticoagulation visits. Hospitalizations, emergency visits, time to reach therapeutic dose, INR $>$ 4, hemorrhagic events, thrombotic events and mortality were secondary endpoints. No difference in the primary endpoints was noted between patients who received initial dosing by clinical and genotype information as compared to those whose initial dosing was determined by clinical information alone. No statistical difference was noted between either group in secondary events, however fewer of these events were noted among patients whose dosing included genotypic data.

GeneSight® Psychotropic Panel Test

Pine Rest Study

The Pine Rest study was a prospective, patient- and rater-blinded, randomized controlled trial evaluating the clinical impact of GeneSight® on antidepressant selection and treatment outcomes in depressed outpatients (GeneSight®, N=25 vs treatment as usual (TAU), N=24). Patients were assessed for symptom improvement, remission and response from baseline (week 0) and at 2, 4, and 8 weeks, using the HAM-D17 rating.

Subjects in the GeneSight® arm had a greater average decrease in the 17-item Hamilton Rating Scale for Depression (HAM-D17) scores from baseline at 8 weeks (p = 0.30) and a higher response rate (p = 0.055) and significantly higher remission rate (p = 0.012) at any time point. Response rates in the GeneSight®-guided arm were 73% higher compared to the unguided TAU arm. Retrospective analysis of the TAU subjects at the end of the study after un-blinding and stratifying by GeneSight® results proved the clinical validity of GeneSight®, with 30% of subjects unknowingly on red bin medications showing a significant worsening of depressive symptoms in contrast to significant improvements in depressive symptoms experienced by 30% of subjects unknowingly on green bin medications (p = 0.07). Additionally, surveys from the treating clinicians revealed that the GeneSight® composite report had a significant influence on treatment decisions for 65% of the GeneSight® subjects.

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Hamm Study

The Hamm Clinic prospective cohort study with two arms (GeneSight® (n = 22) vs. TAU (n = 22)) enrolled adult patients with a primary diagnosis of major depressive disorder utilizing DSM-IV criteria for depression not otherwise specified. GeneSight® subjects achieved greater reductions in depression symptoms between the baseline and the week 8 visits compared to TAU subjects using the Quick Inventory of Depressive Symptomatology – Clinician version (QIDS-C16) (p = 0.0024) and HAM-D17 (p = 0.042) ratings. Both the response and remission rate were more than doubled in the GeneSight® arm compared to the TAU arm. Upon unblinding the TAU group at the end of 8 weeks, TAU subjects were being prescribed significantly more red and yellow bin medications and less green bin medications compared to the GeneSight® guided subjects (p = 0.02).

La Crosse

In the La Crosse prospective cohort study (GeneSight® (n = 72) vs. TAU (n = 93)) at the Franciscan Skemp Hospital in La Crosse, Wisconsin, patients with a primary diagnosis of MDD or depression not otherwise specified with a minimum score of 14 on HAM-D17 were enrolled. Diagnosis was confirmed by checking the diagnosis reported in the physician clinical notes in the electronic medical record (EMR). Samples were collected at baseline in both arms, while only the physicians in the GeneSight® arm were provided with test results to inform treatment decisions. In addition to the prospective comparisons, retrospective analysis in the TAU subjects at the end of the study was implemented after un-blinding the GeneSight® results to test for clinical validity.

A greater reduction in depression scores from baseline to the week 8 visit was observed in the GeneSight® arm for all three measures of depression: QIDS-C16 (p < 0.0001), HAM-D17 (p < 0.0001), and PHQ-9 (p < 0.0001). In all measures, a faster reduction of symptoms was observed in the GeneSight® arm subjects compared to the TAU arm subjects (QIDS-C16 and HAM-D17 (p < 0.0001), PHQ-9 (p = 0.002)). The GeneSight® arm had a significantly higher remission rate based on the QIDS-C16 score (p = 0.03), and significantly higher response rates based on QIDS-C16 (p = 0.005), HAM-D17 (p = 0.03), and PHQ-9 (p = 0.01).

Physicians changed medications more often for subjects in the GeneSight®-guided group (57.9%) than the unguided group (25.9%) (p = 0.0007). Of the 15 GeneSight®-guided subjects classified in the red bin category at baseline, fourteen (93.3%) experienced a medication change or dose adjustment during the eight week study period, compared with 8 out of 18 subjects in the unguided group (44.4%) in the red bin category (p = 0.002). A significant association between bin status and outcome was observed within the unguided group (p = 0.028). Subjects classified in the red bin category had less improvement (11%) eight than those classified in the green or yellow categories (31.9%, p = 0.047), further demonstrating the deleterious effects of red bin medications on patient outcomes.

Dayton Study

This retrospective study, in collaboration with Union Health Services (UHS, a staff model HMO located in Chicago, Illinois), examined healthcare utilization in relation to medication categories (binning) using

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GeneSight®. Ninety-six patients previously diagnosed with a depressive disorder or anxiety disorder and treated with one of the medications included in the GeneSight® panel were included in the study. The GeneSight® bin assignments of patient psychiatric medications were compared to the medical records for patient medication prescriptions, healthcare utilization, medical absence days, and disability claims for the previous 12 months.

Subjects whose medication regimen included a medication in the GeneSight® red bin (“use with caution and more frequent monitoring”) had 69% more total healthcare visits (p = 0.005), 67% more general medical visits (p = 0.02), greater than 3-fold more medical absence days (p = 0.06), and greater than 4-fold more disability claims (p = 0.004) than subjects taking drugs in the green (“use as directed”) or yellow bin (“use with caution”). The mean healthcare utilization cost calculated for red bin subjects during the previous 12 month period was higher at \$8,627, compared to \$3,453 calculated for green bin subjects (p = 0.024) and \$3,426 for yellow bin subjects (p = 0.027), yielding an average annual increase in healthcare cost of \$5,188 for subjects on GeneSight® red bin medications.

Meta-analysis of GeneSight® Prospective 2-Armed Studies

In a meta-analysis of three prospective, 2-armed clinical trials (Pine Rest, Hamm, and La Crosse), use of the test to aid in therapeutic selection has improved patient responses to treatment by 73% on average, which is consistent with the results from each study individually, and is highly significant (p=0.004). These findings support the value of the GeneSight® test in improving patient outcomes.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously

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considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

MEDICAL POLICY CROSS REFERENCES

Providence Health Plans Medical Policies

- Genetic Studies and Counseling, GT234
- Genetic Testing: Hereditary Breast and Ovarian Cancer (Medicare Only), GT380
- Genetic Testing: Inherited Susceptibility to Colorectal Cancer (Medicare Only), GT413
- Genetic Testing: Non-Covered Genetic Panel Tests (Medicare Only), GT420
- Inflammatory Bowel Disease (IBD) Serologic Testing and Therapeutic Monitoring, GT312
- Non-Small Cell Lung Cancer: Molecular Testing for Targeted Therapy (Medicare Only), LAB421

Providence Health Plans Pharmacy Policies

- Brineura. Endocrine & Metabolic Drugs, ORPTCEND049
- Arcalyst®. Miscellaneous Agents, ORPTCOTH005
- Berinert®/Kalbitor®/Ruconest®/Firazyr®. Hematological Agents, ORPTCHEM007
- Cinryze®/Haegarda®. Hematological Agents, ORPTCHEM005
- Chenodal®. Gastrointestinal Agents, ORPTCGAS019
- Exondys 51®. Neuromuscular Drugs, ORPTCNEU020
- Kalydeco®/Orkambi®. Respiratory, ORPTCRES005
- Spinraza®. Neuromuscular, ORPTCNEU021
- Injectable ANTI-Cancer Medications. Antineoplastics, ORPTCONC102
- Oral ANTI-Cancer Medications. Antineoplastics, ORPTCONC103

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