

Department of Origin: Integrated Healthcare Services	Effective Date: 03/21/24
Approved by: Chief Medical Officer	Date Approved: 06/09/23
Clinical Policy Document: Pharmacogenetic / Pharmacogenomic Testing	Replaces Effective Clinical Policy Dated: 08/02/23
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PURPOSE:

The purpose of this clinical policy is to provide guidelines for coverage of *pharmacogenetic/pharmacogenomic* testing for heritable and somatic conditions.

Please refer to the member's benefit document for specific information. To the extent there is any inconsistency between this policy and the terms of the member's benefit plan or certificate of coverage, the terms of the member's benefit plan document will govern.

POLICY:

Benefits must be available for health care services. Health care services must be ordered by a provider. Licensed Genetic Counselors may also order genetic tests if it is within the scope of practice of their state licensure. Health care services must be medically necessary, applicable conservative treatments must have been tried, and the most cost effective alternative must be requested for coverage consideration.

COVERAGE:

- I. After history, physical examination and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain and a valid specific test exists for the suspected condition – as evidenced by all of the following: 1 - 3
 1. Each test has been approved for its intended use by the appropriate *regulatory/oversight body* (implies *analytic validity*); and
 2. Each test has sufficient sensitivity or specificity (*clinical validity*) for targeting the member's specific clinical condition; and
 3. The results of each test will directly impact clinical decision-making and clinical care (*clinical utility*) for the individual.

[Note: Genetic counseling is not required for well-defined populations.]

- II. Requests for *pharmacogenetic/pharmacogenomic* are appropriate, for the member's condition and indication stated in the table in Attachment A, based on the following:
 - A. Is a *companion diagnostic* or required test, as listed on the U.S. Food and Drug Administration (FDA) List of Cleared or Approved Companion Diagnostic Devices (CACDD) or on the package insert under Indications and Usage; or
 - B. Other *reliable evidence*.

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EXCLUSIONS (not limited to):

Refer to member's Certificate of Coverage or Summary Plan Description.

I. The following tests are considered investigative (see Investigative List):

Pharmacogenetic/pharmacogenomic testing for any of the following:

- ABCB1 genotyping to determine drug metabolizer status for all drugs
- ADRA2A genotyping to determine drug metabolizer status for all drugs
- ANKK1 genotyping to determine drug metabolizer status for all drugs
- BDNF genotyping to determine drug metabolizer status for all drugs
- COMT genotyping to determine drug metabolizer status for all drugs
- *Cytochrome P450 (CYP450)* genotyping to detect polymorphisms, including, but not limited to, CYP1A2, CYP2C9, CYP3A4, CYP3A5
 - Does not include the following:
 - CYP2C19 variant(s) for
 - Clopidogrel (Plavix)
 - Use in managing antidepressant and antipsychotic drugs in treatment of depression or generalized anxiety disorder
 - CYP2D6 variant(s) for (revised 12/21)
 - Eliglustat (Cerdelga) in persons with Gaucher disease type 1
 - Tetrabenazine (Xenazine) doses greater than 50mg per day
 - Use in managing antidepressant and antipsychotic drugs in treatment of depression or generalized anxiety disorder
- DRD2 genotyping to determine drug metabolizer status for all drugs
- DPYD gene mutation testing prior initiation of treatment with a fluoropyrimidine medication
- FKBP5 genotyping to determine drug metabolizer status for all drugs
- GRIK4 genotyping to determine drug metabolizer status for all drugs
- HLA-A*31:01 genotyping to determine drug metabolizer status for all drugs
- HLA-B*1502, 15:13 genotyping to determine drug metabolizer status for all drugs except for members of Asian ancestry prior to initiation of treatment with carbamazepine (Tegretol)
- HLA-B*5701 screening except for persons with HIV-1 prior to initiation of treatment with abacavir (Ziagen)
- HTR1A genotyping to determine drug metabolizer status for all drugs
- HTR2A genotyping to determine drug metabolizer status for all drugs
- HTR2C genotyping to determine drug metabolizer status for all drugs
- MC4R genotyping to determine drug metabolizer status for all drugs
- MTHFR genotyping for determining therapeutic response to antifolate chemotherapy and to guide antidepressant therapy
- OPRM1 genotyping to determine drug metabolizer status for all drugs
- SLC6A4 genotyping to determine drug metabolizer status for all drugs
- SLCO1B1 genotyping to determine drug metabolizer status for all drugs
- TXNRD2 genotyping to determine drug metabolizer status for all drugs
- UGT2B15 genotyping to determine drug metabolizer status for all drugs
- VKOR1C genotyping to determine drug metabolizer status for all drugs

II. Direct-to-consumer testing

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DEFINITIONS:

Analytic Validity:

How accurately and reliably the test measures the genotype of interest. A major component in the validation of an analytical technique is the technique's ability to accurately determine the presence of the substance it is seeking. It must measure the target substance without a great range of variation over a number of trials. The technique also must be proven to work reliably at multiple labs to be validated by this testing.

Clinical Utility:

The evidence of improved measurable clinical outcomes, and its usefulness and added value to patient management decision-making compared with current management without the testing.

Clinical Validity:

How consistently and accurately the test detects or predicts the intermediate or final outcomes of interest.

Companion Diagnostic:

A companion diagnostic is a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional determine whether a particular therapeutic product's benefits to patients will outweigh any potential serious side effects or risks. Companion diagnostics can:

- identify patients who are most likely to benefit from a particular therapeutic product;
- identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or
- monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

Cytochrome P450 (CYP450):

The cytochrome P450s (CYPs) are members of a superfamily of oxidative enzymes, which represent the major system for oxidative metabolism of therapeutic substances. Sequencing of the human genome has revealed 58 different human CYP genes, which encode various CYP isoenzymes. CYP enzyme activity can be affected by genetic and environmental factors. One of the more common environmental influences occurs through drug-drug interactions.

Epigenetic changes:

Affect genes without altering the gene sequence. This may occur via changes in gene methylation or histone modification (methylation, acetylation), either of which can influence the rate of transcription or silencing of gene expression. Other epigenetic changes include the alterations in noncoding RNAs and telomere length. These epigenetic changes can be passed on from parents to offspring but can also result from environmental influences on the epigenome. An example of an epigenetic change that affects drug metabolism is reduced sensitivity of a tumor to a chemotherapeutic drug due to gene methylation

Next Generation Sequencing (NGS):

Used to analyze specimens for the four main classes of genomic alterations (base substitutions, insertions and deletions, copy number alterations, and rearrangements)

Pharmacogenetics:

A subcategory of pharmacogenomics that refers to the role of genetic variation on response to a drug. Pharmacogenetics generally is used to refer to a specific DNA polymorphism or coding variant rather than epigenetic or transcriptomic changes across the genome. In practice, pharmacogenetics and pharmacogenomics are often used interchangeably.

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Pharmacogenomics:

The role of various components of the genome on response to a drug. Among the most commonly studied are genetic sequence variants, structural changes in chromosomes (eg, translocations), epigenetic variants (eg, changes in gene methylation), and variation in the expression profile of genes (changes in messenger RNA [mRNA] levels) or noncoding RNA (eg, changes in microRNA). The genetic variation can be inherited through the germline or acquired (eg, somatic mutation in a tumor). The availability of high-throughput techniques to interrogate the entire genome has facilitated many pharmacogenomic studies.

Pharmacokinetics (PK):

Refers to how a drug moves through an individual's body. A drug's PK includes its absorption, distribution, metabolism, and elimination, all of which affect the drug's effect by altering the drug's concentration at its site of action.

Pharmacodynamics:

Refers to an individual's body's therapeutic response to a drug. This generally is determined by the drug's affinity and activity at its site of action, which is often a receptor.

Regulatory/oversight body:

Such as, but not limited to, Clinical Laboratory Improvement Amendments (CLIA), Food and Drug Administration (FDA) or The Joint Commission

Reliable Evidence:

Reliable evidence shall mean consensus opinions and recommendations reported in the relevant medical and scientific literature, peer-reviewed journals, reports of clinical trial committees, or technology assessment bodies, and professional consensus opinions of local and national health care providers.

BACKGROUND:

Pharmacogenomic influences on drug responses have traditionally been divided into four categories based upon the impact of genetic variability on the pharmacologic properties of a drug.

- Effect on drug pharmacokinetics; an example is a genetic variant that alters drug metabolism, affecting plasma concentration.
- Effects on pharmacodynamics; an example is a genetic variation that reduces binding of the drug to its receptor, thereby decreasing therapeutic efficacy.
- Effects on idiosyncratic reactions, such as the likelihood of a hypersensitivity reaction to a certain drug.
- Effects on disease pathogenesis or severity and response to specific therapies; these include specific molecular defects related to the pathogenesis of certain malignancies for which specific targeted therapies have been developed

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Prior Authorization: Yes, per network provider agreement - for those marked with an * on Attachment A

CODING:

CPT® or HCPCS

81120 IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C) (eg, Abbot RealTime IDH1)

81121 IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M) (eg, Abbot RealTime IDH2)

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 arrangements) (eg, BRCAAnalysis CDx, FoundationFocus CDxBRCA)

81163 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

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)

81170 ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain

81206 BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative

81207 BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative

81208 BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, other breakpoint, qualitative or quantitative

81210 BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variants (eg, cobas 4800 BRAF V600 Mutation Test, BRAF V600E and V600K mutation by THxID BRAF)

81220 CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)

81222 CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants

81235 EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg exon 19LREA deletion, L858R, T7090M, G719A, G719S, L81Q) (eg, cobas EGFR Mutation Test v2, theascreen EGFR RQC PCR Kit, DAKO EGFR pharmDX Kit)

81236 EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence) (eg, cobas EZH2 Mutation Test)

81237 EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variants (eg, codon 646) (eg, cobas EZH2 Mutation Test)

81245 FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (i.e., exons 14, 15)

81246 FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)

81272 KIT (v-KIT Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia melanoma), gene analysis, targeted sequence analysis (eg, exons 8,11,13,17,18) (eg, Dako c-Kit pharmDX assay)

81273 KIT (v-KIT Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s) (eg, KIT D816V assay)

81275 KRAS (V-KI-RAS2 Kirsten Rat Sarcoma viral oncogene) gene analysis, variants in codons 12 and 13 (eg, cobas KRAS Mutation Test or KRAS RGQ PCR kit – theascreen)

81283 IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant

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81287 MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis)

81301 Microsatellite instability analysis of markers for mismatch repair deficiency, includes comparison of neoplastic and normal tissue

81306 NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6)

81311 NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61) (eg, cobas KRAS Mutation Test or theascreen KRAS RGQ PCR kit)

81314 PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (e.g., gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)

81306 NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6)

81328 SLC01B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)

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

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)

81350 UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)

81401 Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using non-sequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) (eg, FIP1L1-PDGFRα fusion kinase/CHIC2 allele deletion)

0016U Oncology (hematolymphoid neoplasia) RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation (eg, BCR/ABL1 major and minor breakpoint fusion transcripts)

0022U DNA and RNA targeted sequencing analysis of 1-23 genes associated with non-small cell lung cancer, reported as presence/absence of variants and associated therapies to consider (Oncomine Dx Target Test)

0023U Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.1836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for midostaurin or gilterinib (LeukoStrat CDx FLT3 Mutation Assay)

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 (FoundationOne CDx)

0040U BCR/ABL1 (t[9;22]) 9eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative (MRDx BCR-ABL Test)

0046U FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative (FLT3 ITD by NGS, LabPMM)

0111U RAS detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] (Praxis Extended RAS panel)

0154U Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the 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) utilizing formalin-fixed paraffin-

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embedded urothelial cancer tumor tissue, reported as FGFR gene alteration status (FGFR RGQ RT-PCR Kit)

0155U Oncology (breast cancer), DNA, 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), utilizing formalin-fixed paraffin-embedded breast tumor tissue, reported as PIK3CA gene mutation status (PIK3CA RGQ PCR Kit)

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 (myChoice CDx)

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 (PIK3CA RGQ RT-PCR Kit)

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 (FoundationOne Liquid CDx)

0242U Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements ic, 1 mCi (Guardant360 CDx)

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

0434U Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes

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REFERENCES:

1. Integrated Healthcare Services Process Manual: UR015 Use of Medical Policy and Criteria
2. Clinical Policy: Coverage Determination Guidelines MP/C009
3. Clinical Policy: Laboratory Tests MP/L001
4. Clinical Policy: Molecular Testing, Tumor/Neoplasm Biomarkers MC/L012
5. Clinical Policy: Pharmacogenetic Testing, CYP2C19 and CYP2D6 MC/L027
6. US. Food and Drug Administration. In Vitro Diagnostics. Content current as of: 05/23/23. Retrieved from <https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools> Accessed 06-02-23.
7. Tantisira K, Weiss ST. Overview of pharmacogenomics. (Topic 2904, Version 73.0; last updated: 09/06/22) In: Tirnauer JS and Shah S, eds. *UpToDate*. Waltham, Mass.: UpToDate; 2023. www.uptodate.com. Accessed 06-02-23.
8. Korf BR, Rehm HL. New Approaches to Molecular Diagnosis. *JAMA*. 2013;309(14):1511-1521.
9. Secretary's Advisory Committee on Genetics, Health and Society (SACGHS). Realizing the potential of pharmacogenomics: opportunities and challenges. 2008 March. Department of Health and Human

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Services. Rockville (MD). Retrieved from

https://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/sacghs_pharmacogenomics_report1.pdf. Accessed 06-02-23.

10. Centers for Disease Control and Prevention. Genomic Testing. ACCE Model List of 44 Targeted Questions Aimed at a Comprehensive Review of Genetic Testing. 2010. Retrieved from: https://www.cdc.gov/genomics/gtesting/acce/acce_proj.htm Accessed 06-02-23.
11. Shackelford RE, Whitling NA, McNab P, Japa S, Coppola D. KRAS Testing A Tool for the Implementation of Personalized Medicine. *Genes Cancer*. 2012 July; 3(7-8): 459–466.
12. Alecensa [package insert]. South San Francisco, CA: Genentech USA, Inc; 2021
13. Bosulif [package insert]. New York, NY: Pfizer; 2021
14. Braftovi [package insert]. Boulder, CO: Array BioPharma Inc; 2020
15. Cerdelga [package insert]. Waterford, Ireland: Genzyme Ireland, Ltd.; 2018
16. Cotellic [package insert]. South San Francisco, CA: Genentech USA, Inc.; 2018
17. Gleevec [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2022
18. Iclusig [package insert]. Cambridge, MA: Takeda Pharmaceuticals Company Limited; 2022
19. Kalydeco [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; 2020
20. Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2022
21. Lynparza [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2022
22. Mekinist [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2022
23. Mektovi [package insert]. Boulder, CO: Array BioPharma Inc; 2019
24. Orkambi [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; 2022
25. Plavix [package insert]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi; 2021
26. Rubraca [package insert]. Boulder, CO: Clovis Oncology, Inc.; 2022
27. Rydapt [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021
28. Sprycel [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2021
29. Talzena [package insert]. New York, NY: Pfizer; 2021
30. Tafinlar [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2022
31. Tecentriq [package insert]. South San Francisco, CA: Genentech USA, Inc.; 2022
32. Xenazine [package insert]. Deerfield, IL: Lundbeck; 2017
33. Zelboraf [package insert]. South San Francisco, CA: Genentech USA, Inc.; 2020
34. Trikafta [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; 2021
35. Spinraza [package insert]. Cambridge, MA: Biogen; 2020
36. Zolgensma [package insert]. Bannockburn, IL: AveXis, Inc.; 2022
37. Ayvakit [package insert]. Cambridge, MA: Blueprint Medicines Corporation; 2021
38. Tegretol [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018
39. Ziagen [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2020
40. Lorbrena [package insert]. New York, NY: Pfizer; 2021
41. Jemperli [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2021
42. Vitrakvi [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals; 2021
43. Tibsovo [package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2019
44. Zejula [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2022
45. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2022
46. Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2022
47. Imfinzi [package insert]. Wilmington, DE: AstraZeneca; 2022
48. Xospata [package insert]. Northbrook, IL: Astellas Pharma US, Inc; 2019
49. Truseltiq [package insert]. Brisbane, CA: QED Therapeutics, Inc.; 2021
50. Evrysdi [package insert]. South San Francisco, CA: Genentech, Inc.; 2022
51. Tagrisso [package insert]. Wilmington, DE; AstraZeneca; 2022
52. Vizimpro [package insert]. New York, NY: Pfizer; 2020

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53. FDA table of Pharmacogenomic Biomarkers in Drug Labeling. Content current as of: 02/10/23.

Retrieved from: <https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling> Accessed 06-02-23.

54. National Comprehensive Cancer Network (NCCN) Guidelines. Acute Myeloid Leukemia. AML-J, MS-3, 4, 7, 8. Version 3.2023, 04/05/23. Accessed 06-05-23.

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Attachment A

Revised 08/01/23

Molecular Marker /Test	Indication	Coverage Criteria
ALK		
ALK [D5F3] CDx Assay Ventana - tissue	Drug eligibility	Medically necessary for members who are considering Alecensa (alectinib), Lorbrena (lorlatinib), Xalkori (crizotinib) or Zykadia (ceritinib) for the treatment of non-small cell lung cancer (NSCLC) ⁶
ALK Break Apart Probe FISH Kit Vysis - tissue	Drug eligibility	Medically necessary for members who are considering Alunbrig (brigatinib) or Xalkori (crizotinib) for the treatment of non-small cell lung cancer (NSCLC) ⁶
ALK	Drug eligibility	Medically necessary for members who are considering Keytruda (pembrolizumab) ²⁰ , Opdivo (nivolumab) ⁴⁵ , Tecentriq (atezolizumab) ³¹ or Yervoy (ipilimumab) ⁴⁶ for the treatment of non-small cell lung cancer (NSCLC)
No specific CPT code		
*BCR/ABL1 and/or ABL1		
BCR/ABL1 translocation and breakpoint analysis MRDx BCR-ABL Test - blood CPT 0040U	Drug monitoring	Medically necessary for monitoring treatment of CML with TKIs and identification of CML patients in the chronic phase being treated with Tasigna (nilotinib) ⁶
BCR/ABL1 breakpoint fusion analysis - blood or bone marrow CPTs 81206, 81207, 81208, 0016U	Drug eligibility and monitoring	Medically necessary for members who are considering, already on, or have a history of treatment with Bosulif (bosutinib) for Philadelphia chromosome + (Ph+) CML ¹³ ; or for Gleevec (imatinib) ¹⁷ , Iclusig (ponatinib) ¹⁸ , or Sprycel (dasatinib) ²⁸ for Philadelphia chromosome + (Ph+) ALL or CML (Ph+)
ABL1 CPTs 81170, 81401		
*BRAF		
BRAF V600E and V600K mutation THxID BRAF Kit - tissue CPT 81210	Drug eligibility	Medically necessary for members who are considering treatment with Braftovi (encorafenib) in combination with Mektovi (binimetinib), Mekinist (trametinib), or Tafinlar (dabrafenib) for the treatment of melanoma. ⁶
BRAF V600 mutation cobas 4800 BRAF V600 Mutation Test – tissue CPT 81210	Drug eligibility	Medically necessary for members who are considering Cotellic (cobimetinib) in combination with Zelboraf (vemurafenib), or Zelboraf alone, for the treatment of melanoma. ⁶

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*BRAF (continued)		
BRAF V600E RCQ PCR Kit theascreen - tissue	Drug eligibility	Medically necessary for members who are considering treatment with Braftovi (encorafenib) in combination with Erbitux (cetuximab) for treatment of colorectal cancer ⁶
BRAF	Drug eligibility	Medically necessary for members who are considering Zelboraf (vemurafenib) ³³ for the treatment of Erdheim-Chester disease Medically necessary for members who are considering Mekinist (trametinib) ²² in combination with Tafinlar (dabrafenib) ³⁰ for the treatment of non-small cell lung cancer Medically necessary for members who are considering Mekinist (trametinib) ²² in combination with Tafinlar (dabrafenib) ³⁰ for the treatment of anaplastic thyroid cancer (ATC) Medically necessary for members who are considering Mekinist (trametinib) ²² in combination with Tafinlar (dabrafenib) ³⁰ for solid tumors
CPT 81210		
*BRCA		
BRCA mutations BRCAAnalysis CDx Myriad (germline mutation) - blood	Drug eligibility	Medically necessary for members who are considering Lynparza (olaparib) or Talzenna (talazoparib) for the treatment of breast cancer ⁶ Medically necessary for members who are considering Lynparza (olaparib) or Rubraca (rucaprib) for the treatment of ovarian (including fallopian tube and primary peritoneal) cancer ⁶ Medically necessary for members are considering Lynparza (olaparib) for the treatment of pancreatic cancer ⁶ Medically necessary for members are considering Lynparza (olaparib) for the treatment of metastatic castration resistant prostate cancer (mCRPC) ⁶
CPT 81162		

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*BRCA (continued) BRCA mutations FoundationFocus CDxBRCA Assay - tissue CPT 81162 BRCA mutations myChoice CDx Myriad - tissue CPT 0172U BRCA - tissue or blood (germline) CPTs 81162, 81163, 81164	Drug eligibility Drug eligibility Drug eligibility	Medically necessary for members who are considering Rubraca (rucaprib) for the treatment of ovarian (including fallopian tube and primary peritoneal) cancer ⁶ Medically necessary as an aid in identifying ovarian (including fallopian tube and primary peritoneal) cancer patients who are candidates for therapy with Lynparza (olaparib) or Zejula (niraparib) ⁶ Medically necessary for members who are considering Lynparza (olaparib) ²¹ or Talzenna (talazoparib) ²⁹ for the treatment of breast cancer Medically necessary for members who are considering Rubraca (rucaprib) ²⁶ or Zejula (niraparib) ⁴⁴ for the treatment of ovarian (including fallopian tube and primary peritoneal) cancer Medically necessary for members who are considering Rubraca (rucaprib) ²⁶ for the treatment of metastatic castration resistant prostate cancer (mCRPC)
CFTR F508del, G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, and S549R mutations – blood CFTR F508del CPTs 81220, 81222	Drug eligibility Drug eligibility	Medically necessary for members who are considering Kalydeco (ivacaftor) ¹⁹ or Orkambi (lumacaftor/ivacaftor) ²⁴ for the treatment of cystic fibrosis Trikafta (elexacaftor, tezacaftor and ivacaftor) for the treatment of cystic fibrosis ³⁴
*EGFR EGFR T790 mutation, exon 19 deletion or exon 21 (L858R) substitution mutations EGFR Mutation Test v1, v2 cobas – tissue or blood CPT 81235	Drug eligibility	Medically necessary for testing of members who are considering a tyrosine kinase inhibitor, eg, Gilotrif (afatinib), Iressa (gefitinib), Tagrisso (osimertinib), Tarceva (erlotinib) or Vizimpro (dacomitinib) for the treatment of non-small cell lung cancer (NSCLC) ⁶

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<p>*EGFR (continued)</p> <p>EGFR T790 mutation, exon 19 deletion or exon 21 (L858R), L862Q, G719X or S7681 substitution mutations EGFR RGQ PCR Kit theascreen – tissue or blood CPT 81235</p> <p>EGFR T790 mutation, exon 19 deletion or exon 21 (L858R) substitution mutations DAKO EGFR pharmDX Kit - tissue CPT 81235</p> <p>EGFR - tissue or blood</p> <p>CPT 81235</p>	<p>Drug eligibility</p> <p>Drug eligibility</p> <p>Drug eligibility</p>	<p>Medically necessary for testing of members who are considering Gilotrif (afatinib), Iressa (gefitinib) or Vizimpro (dacomitinib) for the treatment of non-small cell lung cancer (NSCLC)⁶</p> <p>Medically necessary for members who are considering Erbitux (cetuximab) or Vectibix (panitumumab) for the treatment of colorectal cancer⁶</p> <p>Medically necessary for testing of members who are considering Keytruda (pembrolizumab) ²⁰, Opdivo (nivolumab)⁴⁵ Tecentriq (atezolizumab)³⁴ or Yervoy (ipilimumab)⁴⁶ for the treatment of non-small cell lung cancer (NSCLC)</p>
<p>*EZH2</p> <p>EZH2 Mutation Test cobas– tissue</p> <p>CPTs 81236, 81237</p>	<p>Drug eligibility</p>	<p>Medically necessary for members who are considering treatment with Tazverik (tazemetostat) for the treatment of follicular lymphoma⁶</p>
<p>*FGFR3</p> <p>Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the 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) FGFR RGQ RT-PCR Kit theascreen - tissue</p>	<p>Drug eligibility</p>	<p>Indicated for use as an aid in identifying urothelial cancer (UC) patients who harbor these alterations and are therefore eligible for treatment with Balversa (erdafitinib)⁶</p>

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CPT 0154U		
<p>*FLT3</p> <p>FLT mutations by FLT3 Mutation Assay to detect internal tandem duplication (ITD) mutations and the tyrosine kinase domain mutations D835 and I836 in the FLT3 gene LeukoStrat CDx - blood or bone marrow CPT 0023U</p> <p>FLT ITD MRD (minimal residual disease) NGS LabPMM - blood or bone marrow CPT 0046U</p> <p>FLT mutations - blood or bone marrow</p> <p>CPTs 81245, 81246</p>	<p>Drug eligibility</p> <p>Monitoring</p> <p>Prognostic, drug eligibility or monitoring</p>	<p>Medically necessary for members who are considering Rydapt (midostaurin) or Xospata (gilteritinib) for the treatment of acute myelogenous/myeloid leukemia (AML)⁶</p> <p>Medically necessary for members who receiving treatment for acute myelogenous/myeloid leukemia (AML)⁵⁴</p> <p>Medically necessary for members who are diagnosed with, considering treatment, or receiving treatment for acute myelogenous/ myeloid leukemia (AML)⁵⁴</p>
<p>*FIP1L1-PDGFRα fusion kinase/ CHIC2 allele deletion - blood</p> <p>CPT 81401</p>	Drug eligibility	Medically necessary for members who are considering Gleevec (imatinib) for the treatment of hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) ¹⁷
<p>FOLR1 Ventana Rx Dx Assay</p> <p>No specific CPT</p>	Drug eligibility	Medically necessary for members who considering treatment with Elahere (mirvetuximab soravtansine-gynx) for the treatment of ovarian cancer (includes fallopian tube and primary peritoneal) ⁶

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* FoundationOne CDx Substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB) and group-based companion diagnostic for BRAF inhibitors and BRAF/MEK inhibitor combinations approved by the FDA - tissue	Drug eligibility	Medically necessary for members who are considering the following drugs for the corresponding cancer conditions Breast cancer ⁶ <ul style="list-style-type: none"> • Herceptin (trastuzumab) • Kadcyca (ado-trastuzumab) • Perjeta (pertuzumab) • Piqray (alpelisib) Cholangiocarcinoma ⁶ <ul style="list-style-type: none"> • Pemazyre (pemigatinib) • Truseltiq (infigratinib) Colorectal cancer ⁶ <ul style="list-style-type: none"> • Erbitux (cetuximab) • Vectibix (panitumumab) Melanoma ⁶ <ul style="list-style-type: none"> • Braftovi (encorafenib) in combination with Mektovi (binimetinib) • Cotellic (cobimetinib) in combination with Zelboraf (vemurafenib) • Mekinist (trametinib) • Tafinlar (dabrafenib) • Tafinlar (dabrafenib) in combination with Mekinist (trametinib) • Tecentriq (atezolizumab) combination with Cotellic (cobimetinib) and Zelboraf (vemurafenib) • Zelboraf (vemurafenib) Non-small cell lung cancer (NSCLC) <ul style="list-style-type: none"> • Alecensa (alectinib)⁶ • Gilotrif (afatinib)⁶ • Iressa (gefinitinib)⁶ • Opdivo (nivolumab)⁴⁵ • Rozlytrek (entrectinib)⁶ • Tafinlar (dabrafenib) in combination with Mekinist (trametinib)⁶ • Tagrisso (osimertinib)⁶ • Tarceva (erlotinib)⁶ • Tecentriq (atezolizumab)³¹ • Trabecta (capmatinib)⁶
CPT 0037U *FoundationOne CDx (continued) Foundation Medicine - tissue	Drug eligibility	

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<p>CPT 0037U</p> <p>*FoundationOne CDx (continued)</p> <p>CPT 0037U</p>	Drug eligibility	<ul style="list-style-type: none"> • Xalkori (crizotinib)⁶ • Vizimpro (dacomitinib)⁶ • Yervoy (ipilimumab)⁴⁶ • Zykadia (ceritinib)⁶ <p>Ovarian cancer (includes fallopian tube and primary peritoneal)⁶</p> <ul style="list-style-type: none"> • Lynparza (olaparib) • Rubraca (rucaparib) <p>Prostate cancer, metastatic castration resistant</p> <ul style="list-style-type: none"> • Lynparza (olaparib)⁶ <p>Solid tumors (MSI-High)⁶</p> <ul style="list-style-type: none"> • Keytruda (pembrolizumab) <p>Solid tumors (NTRK1/2/3 fusions)⁶</p> <ul style="list-style-type: none"> • Rozlytrek (entrectinib) • Vitrakvi (larotrectinib) <p>Solid tumors (TMB≥ 10 mutations per megabase)⁶</p> <ul style="list-style-type: none"> • Keytruda (pembrolizumab)
<p>*FoundationOne Liquid CDx Foundation Medicine – blood</p> <p>Utilizes circulating cell-free DNA (cfDNA)</p> <p>CPT 0239U</p>	Drug eligibility	<p>Medically necessary for members who are considering the following drugs for the corresponding cancer conditions⁶</p> <p>Breast cancer</p> <ul style="list-style-type: none"> • Piqray (alpelisib) <p>Non-small cell lung cancer (NSCLC)</p> <ul style="list-style-type: none"> • Alecensa (alectinib) • Exkivity (mobocertinib) • Iressa (gefitinib) • Rozlytrek (entrectinib) • Tagrisso (osimertinib) • Tarceva (erlotinib) • Trabrecta (capmatinib) <p>Ovarian cancer (includes fallopian tube and primary peritoneal): Rubraca (rucaparib)</p> <p>Prostate cancer, metastatic castrate resistant (mCRPC)</p> <ul style="list-style-type: none"> • Lynparza (olaparib) • Rubraca (rucaparib)

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		Solid Tumors <ul style="list-style-type: none"> Rozlytrek (entrectinib)
*Guardant360 CDx Guardant Health – blood CPT 0242U	Drug eligibility	Medically necessary for members who are considering the following drugs for corresponding cancer condition ⁶ Breast cancer <ul style="list-style-type: none"> Orserdu (elacestrant) Non-small cell lung cancer (NSCLC) <ul style="list-style-type: none"> Enhertu (fam-trastuzumab derustecan-nxki) Lumakras (sotorasib) Rybrevant (amivantamab-vmjw) Tagrisso (osimertinib)
HER-2/NEU HER2 IHC Bond Oracle, HER2CISH pharmDx Kit, HercepTest, INFORM HER2 Dual ISH DNA probe, INFORM HER-2/neu, InSite HER-2/neu (CB11), PathVysion HER-2 DNA probe, PATHWAY anti-Her2/neu, SPOT-LIGHT HER2 CISH Kit, HER2 FISH pharmDX Kit, CPTs 83950,88342,88365 HER2 DEPAarray HER2–tissue CPT 0009U	Prognostication, drug eligibility Prognostication, drug eligibility	Indicated as an aid in the assessment of patients for whom treatment is being considered for the cancer conditions listed ⁶ Breast cancer <ul style="list-style-type: none"> Herceptin (trastuzumab) Kadcyla (ado-trastuzumab emtansine) Perjeta (pertuzumab) Gastric and gastroesophageal cancer <ul style="list-style-type: none"> Herceptin (trastuzumab)
HLA HLA-A*02:01 HLA-B*1502 HLA-B*5701 HLA-B*58:01 CPTs 81370-81383	Drug eligibility Drug eligibility Drug eligibility Drug eligibility	Medically necessary for members who are considering Kimmtrak (tebentafusp-tebn) for uveal melanoma ⁶ Indicated for persons of Asian ancestry before initiating treatment with Tegretol (carbamazepine) ³⁸ Indicated for persons with HIV-1 before initiating treatment with Ziagen (abacavir) ³⁹

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		Indicated in Asian persons prior to commencing allopurinol therapy ⁵³
*IDH1 IDH1 R132 mutations (R132C, R132H, R132G, R132S, and R132L) Abbott RealTime - blood or bone marrow CPT 81120	Drug eligibility	Medically necessary for members who are considering Rezlidhia (olutasidenib) or Tibsovo (ivosidenib) for the treatment of acute myeloid leukemia (AML) ⁶
*IDH2 IDH2 mutations (R140Q, R140L, R140G, R140W, R172K, R172M, R172G, R172S, and R172W) by Abbott RealTime - blood or bone marrow CPT 81121	Drug eligibility	Medically necessary for members who are considering Idhifa (enasidenib) for the treatment of acute myeloid leukemia (AML) ⁶
Ki-67 IHC MIB-1 pharmDx - tissue No specific CPT	Drug eligibility	Medically necessary for members who are considering Verzenio (abemaciclib) for the treatment of breast cancer ⁶
*C- Kit protein/CD 117 antigen c-Kit pharmDX Assay Dako- tissue CPT 81272	Drug eligibility	Medically necessary for members who are considering Gleevec/Glivac (imatinib mesylate) for the treatment of gastrointestinal stromal tumors (GIST) and to aid in the differential diagnosis of GIST ⁶
*KIT D816V assay for the kit d816v mutation - bone marrow CPT 81273	Drug eligibility	Medically necessary for members who are considering Gleevec (imatinib mesylate) for the treatment of aggressive systemic mastocytosis (ASM) ⁶

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<p>*KRAS/NRAS codons 12 and 13 mutations cobas KRAS Mutation Test or KRAS RGQ PCR kit theascreen - tissue</p> <p>CPTs 81275, 81311</p> <p>KRAS G12C NGS panel Agilent Resolution CtDx FIRST assay – blood CPT 0397U</p>	<p>Drug eligibility</p> <p>Drug eligibility</p>	<p>Medically necessary for members who are considering Erbitux (cetuximab) or Vectibix (panitumumab) for the treatment of colorectal cancer⁶</p> <p>Medically necessary for members who are considering Krazati (adagrasib) or Lumakras (sotorasib) for the treatment of NSCLC⁶</p> <p>Medically necessary for members who are considering Krazati (adagrasib) for the treatment of NSCLC⁶</p>
<p>*Microsatellite instability-high (MSH-H) or mismatch repair (MMR) genes - tissue</p> <p>CPT 81301</p>	<p>Drug eligibility</p>	<p>Medically necessary for members who are considering Keytruda (pembrolizumab), for the treatment of solid tumors or colorectal cancer²⁰</p> <p>Medically necessary for members who are considering Opdivo (nivolumab)⁴⁵ or Yervoy (ipilimumab)⁴⁶ for the treatment of colorectal cancer</p>
<p>*Mismatch repair (MMR) genes MLH-1, PMS2, MSH2, MSH6 Ventana MMR RxDx panel - tissue</p> <p>CPT 81445</p>	<p>Drug eligibility</p>	<p>Medically necessary for members who are considering Jemperli (dostarlimab-gxly) for the treatment of endometrial carcinoma⁶</p> <p>Medically necessary for members who are considering Jemperli (dostarlimab-gxly) or Keytruda (pembrolizumab) for mismatch repair deficient (dMMR) solid tumors⁶</p> <p>Medically necessary for members who are considering Keytruda (pembrolizumab) in combination with Lenvima for endometrial carcinoma⁶</p>
<p>*ONCO/Reveal Dx Lung & Colon Cancer Assay KRAS wild-type (absence of mutations in codons 12 and 13) EGFR Exon 19 deletions and Exon 21 L858R</p>	<p>Drug eligibility</p>	<p>Medically necessary for members who are considering Erbitux (cetuximab) or Vectibix (panitumumab) for the treatment of colorectal cancer⁶</p> <p>Medically necessary for members who are considering an EGFR Tyrosine Kinase</p>

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substitution mutations – tissue No specific CPT		Inhibitor that is approved by the FDA for NSCLC ⁶ <ul style="list-style-type: none"> • Gilotrif (afatinib)⁶ • Iressa (gefitinib)⁶ • Tagrisso (osimertinib)⁶ • Tarceva (erlotinib)⁶ • Vizimpro (dacomitinib)⁶
*Oncomine Dx Target Test Single nucleotide variants (SNVs) and deletions in 23 genes from DNA and fusions in ROS1, BRAF V600E, ROS1 fusions and EGFR L858R, Exon 19 deletions - tissue CPT 0022U	Drug eligibility	Medically necessary for members who are considering the following drugs for the corresponding cancer conditions: Cholangiocarcinoma ⁶ <ul style="list-style-type: none"> • Tibsovo (ivosidenib) Non-small cell lung cancer (NSCLC) ⁶ <ul style="list-style-type: none"> • Enhertu (fam-trastuzumab derustecan-nxki) • Exkivity (mobocertinib) • Gavreto (pralsetinib) • Iressa (gefitinib) • Retevmo (selpercatinib) • Rybrevant (amivantamab-vmjw) • Tafenlar (dabrafenib) in combination with Mekinist (trametinib) • Xalkori (crizotinib) Thyroid cancer (includes medullary) ⁶ <ul style="list-style-type: none"> • Retevmo (selpercatinib)
PD-L1 PD-L1 by IHC 22C3 pharmDX - tissue PD-L1 IHC 28-8 pharmDX - tissue	Drug eligibility Drug eligibility	Medically necessary for members who are considering Keytruda (pembrolizumab) ⁶ for the following: <ul style="list-style-type: none"> • Cervical cancer • Esophageal squamous cell carcinoma (ESCC) • Head and neck squamous cell carcinoma (HNSCC) • Non-small cell lung cancer (NSCLC) • Triple negative breast cancer (TNBC) Medically necessary for members who are considering Libtayo (cemiplimab-rwlc) for <ul style="list-style-type: none"> • Non-small cell lung cancer (NSCLC)⁶ Medically necessary for members who are considering Opdivo (nivolumab) in combination with Yervoy (ipilimumab) for:

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PD-L1 (SP142) CDx Assay Ventana - tissue	Drug eligibility	<ul style="list-style-type: none"> Non-small cell lung cancer (NSCLC)⁶ <p>Medically necessary for members who are considering Tecentriq (atezolizumab) for the treatment of non-small cell lung cancer (NSCLC)⁶</p> <p>Medically necessary for members who are considering Tecentriq (atezolizumab) for the treatment of urothelial carcinoma⁶</p>
PD-L1 (SP263) CDx Assay Ventana - tissue	Drug eligibility	Medically necessary for members who are considering Tecentriq (atezolizumab) for the treatment of non-small cell lung cancer (NSCLC) ⁶
No specific CPT		
* PDGFRα exon 18 mutation, including PDGFRA D842V tissue	Drug eligibility	Medically necessary to determine eligibility for Ayvakit (avapritinib) for gastrointestinal stromal tumor (GIST) ³⁷
CPT 81314		
PDGFRβ gene rearrangement PDGFRβ FISH Assay - bone marrow	Drug eligibility	Medically necessary for members who are considering Gleevec (imatinib) for the treatment of chronic myelomonocytic leukemia or myelodysplastic syndrome/myeloproliferative disease (MDS/MPD) ⁶
No specific CPT		
* PIK3CA		
PIK3CA RGQ PCR Kit therascreen tissue - CPT 0155U blood - CPT 0177U	Drug eligibility	Medically necessary to detect the presence of one or more PIK3CA mutations in members with breast cancer to determine if they are eligible for treatment with Piqray (alpelisib) ⁶
* RAS detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] Praxis Extended RAS panel - tissue	Drug eligibility	Medically necessary for members considering Vectibix (panitumumab) for the treatment of colorectal cancer ⁶
CPT 0111U		

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SMN 1 and 2 deletions/mutations CPTs 81329, 81336, 81337, 0236U	Drug eligibility	Medically necessary for members considering Evrysdi (risdiplam) ⁵⁰ , Spinraza (nusinersen) ³⁵ or Zolgensma (onasemnogene abeparvovec-xioi) ³⁶ for the treatment of spinal muscular atrophy
TP53 LSI TP53 probe target (17p-) Vysis CLL FISH PROBE Kit - blood No specific CPT code	Drug eligibility	Medically necessary for members who are considering Venclexta (venetoclax) for the treatment of B-cell chronic lymphocytic leukemia (CLL) ⁶
xT CDx Tempus Labs – matching blood and saliva No specific CPT code	Drug eligibility	Medically necessary for members who are considering Erbitux (cetuximab) or Vectibix (panitumumab) for the treatment of colorectal cancer ⁶

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Provides free aids and services to people with disabilities to communicate effectively with us, such as:

- Qualified sign language interpreters
- Written information in other formats (large print, audio, accessible electronic formats, other formats)

Provides free language services to people whose primary language is not English, such as:

- Qualified interpreters
- Information written in other languages

If you need these services, contact a Grievance Specialist.

If you believe that PCHP has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Grievance Specialist
PreferredOne Community Health Plan
PO Box 59052
Minneapolis, MN 55459-0052
Phone: 1.800.940.5049 (TTY: 763.847.4013)
Fax: 763.847.4010
customerservice@preferredone.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, a Grievance Specialist is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

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ATTENTION: If you do not speak English, language assistance services, free of charge, are available to you. Call 1.800.940.5049 (TTY: 763.847.4013).

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1.800.940.5049 (TTY: 763.847.4013).

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ໂປດຊາບ: ຖ້າວ່າທ່ານເວົ້າພາສາລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ເສຍຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທ 1.800.940.5049 (TTY: 763.847.4013).

ማስታወሻ: የሚገኙት ቋንቋ አማርኛ ከሆነ የትርጉም እርዳታ ድርጅቶች፣ በነጻ ሊያግኝዎት ተዘጋጅተዋል፡ ወደ ሚከተለው ቁጥር ይደውሉ፡ 1.800.940.5049 (መለስማት ለተሳናቸው፡ 763.847.4013)፡

ဟ်သ့ဟ်သး- နမၤကတိၤ ကသီၤ ကျိၣ်အယိၤ, နမၤန့ၣ် ကျိၣ်အတၢ်မၤစၢၤလၢ တလၢၣ်ဘျဉ်လၢၣ်စၢၤ နီၣ်တမံၤဘၣ်သ့န့ၣ်လီၤ. ကိး 1.800.940.5049 (TTY: 763.847.4013).

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ប្រយ័ត្ន៖ បើសិនជាអ្នកនិយាយ ភាសាខ្មែរ, សេវាជំនួយផ្នែកភាសា ដោយមិនគិតល្បួល គឺអាចមានសំរាប់បំរើអ្នក។ ចូរទូរស័ព្ទ 1.800.940.5049 (TTY: 763.847.4013)។

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PIC:

Provides free aids and services to people with disabilities to communicate effectively with us, such as:

- Qualified sign language interpreters
- Written information in other formats (large print, audio, accessible electronic formats, other formats)

Provides free language services to people whose primary language is not English, such as:

- Qualified interpreters
- Information written in other languages

If you need these services, contact a Grievance Specialist.

If you believe that PIC has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Grievance Specialist
PreferredOne Insurance Company
PO Box 59212
Minneapolis, MN 55459-0212
Phone: 1.800.940.5049 (TTY: 763.847.4013)
Fax: 763.847.4010
customerservice@preferredone.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, a Grievance Specialist is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

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បំពេញ: ប្រសិនបើ អ្នកនិយាយភាសាខ្មែរ, សេវាជំនួយភាសា ដោយមិនគិតថ្លៃ គឺអាចមានសំរាប់អ្នក។ ហៅ 1.800.940.5049 (TTY: 763.847.4013).

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ဟံသာဝတီ: နမူနာတို့ ကညီ ကျိအသိ, နမူနာ ကျိအတိအကျတို့ တလက်ကွက်လက်စွာ နှိတ်မိသည့်သို့လိ။ ကိ: 1.800.940.5049 (TTY: 763.847.4013).

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