PreferredOne®

Department of Origin: Integrated Healthcare Services	**Approved by:** Chief Medical Officer	**Date Approved:** 12/19/17
Department(s) Affected: Claims, Coding, Customer Service, Integrated Healthcare Services	**Effective Date:** 01/03/18	
Medical Policy Document: Molecular Testing: Tumor/Neoplasm Biomarkers	**Replaces Effective Policy Dated:** 01/03/18	
Reference #: MP/M001	**Page:** 1 of 18	

PRODUCT APPLICATION:
☒ PreferredOne Community Health Plan (PCHP)
☒ PreferredOne Administrative Services, Inc. (PAS) ERISA
☒ PreferredOne Administrative Services, Inc. (PAS) Non-ERISA
☒ PreferredOne Insurance Company (PIC) Individual
☒ PreferredOne Insurance Company (PIC) Large Group
☒ PreferredOne Insurance Company (PIC) Small Group

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.

Benefits must be available for health care services. Health care services must be ordered by a physician, physician assistant, or nurse practitioner. 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.

This policy applies to PAS members only when the employer group has elected to provide benefits for the services involved. Check benefits in SPD. If benefits not specifically addressed in the SPD, verify the availability of benefits with the appropriate account manager.

PURPOSE:
The purpose of this policy is to provide coverage guidelines for molecular based testing on tissue or body fluid.

POLICY:
PreferredOne covers medically necessary molecular testing when the *analytic* and *clinical validity* of the test have been established and the *clinical utility* of the test is supported by *reliable evidence* showing that using the test will significantly guide subsequent testing and/or treatment and lead to clinically meaningful improvement in outcomes.

PreferredOne adopts National Comprehensive Cancer Network (NCCN coverage determinations for requests for these services. On the occasion PreferredOne receives a request for a test that is not addressed by NCCN, PreferredOne will assess National Committee for Quality Assurance (NCQA) accredited health plan(s) coverage positions and may choose to seek its own coverage position seeking *reliable evidence* and following the PreferredOne expert opinion and Quality Management Subcommittee oversight process.

GUIDELINES:
Medical Necessity Criteria - Must satisfy: I and one of II or III; apply IV when applicable

I. General characteristics of covered tests - must meet all of: A-C

   A. Each test has been approved for its intended use by the appropriate regulatory/oversight body (implies *analytic validity*); and

   B. Each test has sufficient sensitivity and specificity (*clinical validity*) for targeting the member's specific clinical condition; and

C. The results of each molecular test will directly impact clinical decision-making and clinical care (*clinical utility*) for the individual; and

II. Request for use of gene-expression profiling meets MC/L012 Gene Expression Profiling; or

III. Each test requested is appropriate, based on the condition and indication stated in the table in Attachment A, which is based on the following: A or B

A. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®); or

B. A National Committee for Quality Assurance (NCQA) accredited health plan(s) coverage position or other *reliable evidence*, when a coverage position is not found in NCCN Guidelines®.

IV. Requests for testing of multiple markers are covered only for the number of tests deemed medically necessary to establish a diagnosis.

EXCLUSIONS:
Either of the following: I or II

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

A. Chemotherapy/ Chemosensitivity/ Tumor Resistance Assay Testing, such as but not limited to, ChemoFX Assay, except for use in recurrent ovarian cancer disease with two or less previous chemotherapy regimens, and re-biopsy of tissue.

B. Topographic Genotyping, PathfinderTG® from RedPath Integrated Pathology

C. Gene expression profiling for breast cancer, such as, but not limited to all of the following (see Investigative List):
- 41-gene signature assay
- BluePrint® (80-gene profile)
- Breast Cancer Gene Expression Ratio (also known as Theros H/ISM)
- Breast Cancer Index℠
- BreastNext™
- BreastOncPx™ or Breast Cancer Prognosis Gene Expression Assay
- BreastPRS
- Genomic Grade Index (also known as MapQuant Dx™)
- EndoPredict®
- HERmark® Breast Cancer Assay
- InsightTM DX Breast Cancer Profile
- MammaPrint® (also known as Amsterdam signature or 70-gene signature)
- Mammostrat™
- NexCourse® Breast IHC4
- Oncotype DX® DCIS
- PAM50 Breast Cancer Intrinsic Classifier™
- Prosigna™ Breast Cancer Prognostic Gene Signature Assay

- SYMPHONY™ Genomic Breast Cancer Profile
- TargetPrint®
- Rotterdam signature assay (76-gene assay)

D. Gene expression profiling/molecular testing for cancers of unknown primaries/occult primary tumors, such as, but not limited to all of the following (see Investigative List):
- CancerTYPE ID® Test
- ProOnc TumorSourceDX™ Test
- ResponseDX: Tissue of Origin Test™ (Pathwork® Tissue of Origin)
- Rosetta Cancer Origin Test™ (miRview® mets and miRview® mets2 tests)

E. Gene expression profiling/molecular testing for colorectal cancer, such as, but not limited to all of the following (see (Investigative List):
- ColDx
- ColoPrint
- Colorectal Cancer DSA®
- GeneFx Colon®
- OncoDefender-CRC®
- Oncotype DX® Colon Cancer Assay

F. Gene expression profiling/molecular testing for predicting malignancy in women with adnexal mass, such as, but not limited to all of the following (see Investigative List):
- OVA1
- Risk of Ovarian Malignancy Algorithm (ROMA)

G. Gene expression profiling/molecular testing for prostate cancer, such as, but not limited to all of the following (see Investigative List):
- TMPRSS:ERG (Transmembrane protease, serine: ERG [ETS related gene] fusion genes for diagnosis and prognosis of prostate cancer (eg, ProstaVysion®)
- Decipher® Prostate Cancer Classifier

[Note: Refer to Attachment A of this policy and medical criteria MC/L012 Gene Expression Profiling Guidelines, for medically necessary indications for the following molecular tests for breast and prostate cancer Oncotype DX® Breast Cancer Assay, 4KScore®, gene hypermethylation of gene regions GSTP1, APC, and RASSF1 (ConfirmMDx™), PCA3, Percent free PSA, Prolaris™ assay, Prostate Health Index (PHI), or the Oncotype DX® Prostate Cancer Assay.]

II. Direct-to-consumer testing

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.

Biomarker:
Any characteristic of an organism that can be objectively measured and evaluated to indicate the presence of a disease or drug reaction.

Clinical Utility:
How likely the test is to significantly improve patient outcomes. 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.

Molecular Testing in Oncology:
Procedures designed to detect somatic or germline mutations in DNA and changes in gene or protein expression that could impact diagnosis, prognosis, prediction, and evaluation of therapy of patients with cancer.

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.

Tumor Marker:
A biomarker that can identify a specific malignancy.

BACKGROUND:
Personalized medicine in oncology is maturing and evolving rapidly and the use of molecular biomarkers in clinical decision-making is growing. This raises important issues regarding the safe, effective, and efficient deployment of molecular tests to guide appropriate care, specifically regarding laboratory-developed tests and companion diagnostics.

Tumor markers are substances produced by cancer or other cells in the body in response to cancer, or certain benign conditions. Most tumor markers are proteins but may also be patterns of gene expression and changes to DNA. Tumor markers are made by normal cells but are produced at a much higher level in the presence of a cancer. Tumor markers may be found in the blood, plasma, other bodily fluids (eg, urine, saliva, sputum, cerebrospinal fluid, or effusions) and/or tissue. Although an abnormal tumor marker level may suggest cancer, their presence alone does not confirm a diagnosis. Tumor markers are typically combined with other diagnostic studies (e.g., laboratory test, biopsy, radiological imaging) to confirm the diagnosis. These markers may not be elevated in the presence of some diseases or cancers, especially in early stages of the disease, may not be specific to a particular type of disease or cancer, and/or may be elevated by more than one type of disease or cancer.

In some types of cancers, tumor marker levels may reflect the extent or stage of the disease and can be useful in determining the most effective treatment and how well the disease will respond to the treatment. Typically, the primary use of tumor markers is to monitor a cancer's response to treatment with periodic measurements following therapy. Following therapy, a decrease in the marker level may indicate a response to therapy as opposed to consistently elevated or rising marker levels which may be indicative of a lack of response to treatment or recurrence of the disease. The evidence in the published peer-reviewed literature and professional societies support tumor makers for the diagnosis and management of some cancers, while other tumor markers are still evolving and their clinical utility has not been proven.

PreferredOne®

Department of Origin: Integrated Healthcare Services	**Approved by:** Chief Medical Officer	**Date Approved:** 12/19/17
Department(s) Affected: Claims, Coding, Customer Service, Integrated Healthcare Services	**Effective Date:** 01/03/18	
Medical Policy Document: Molecular Testing: Tumor/Neoplasm Biomarkers	**Replaces Effective Policy Dated:** 01/03/18	
Reference #: MP/M001	**Page:** 5 of 18	

FOR INTERNAL USE ONLY

COVERAGE:
Prior Authorization: Yes - for those marked with an *

Coverage is subject to the member's contract benefits.

CODING: See Attachment A

RELATED CRITERIA/POLICIES:
Integrated Healthcare Services Process Manual: UR015 Use of Medical Policy and Criteria
Medical Criteria: MC/L012 Gene Expression Profiling
Medical Policy: MPC003 Criteria Management and Application
Medical Policy: MP/C009 Coverage Determination Guidelines
Medical Policy: MP/L001 Laboratory Tests
Medical Policy: MP/P013 Pharmacogenetic/Pharmacogenomic Testing and Serological Testing for Inflammatory Conditions

REFERENCES
1. American Association for Clinical Chemistry (AACC). Tumor Markers. Accessed Sept 18, 2013. Available at URL address: http://www.labtestsonline.org/understanding/analytes/tumor_markers/glance-3.html
2. American Cancer Society (ACS). Tumor Markers. Mar 24, 2011. Accessed Sept 18, 2013. Available at URL address: http://www.cancer.org/acs/groups/cid/documents/webcontent/003189-pdf.pdf
3. National Cancer Institute (NCI). Tumor markers: 2011. Accessed Sept 18, 2013. Available at URL address: http://www.cancer.gov/cancertopics/factsheet/Detection/tumor-markers
4. Engstrom PF, et. al. National Comprehensive Cancer Network (NCCN). NCCN Molecular Testing White Paper: Effectiveness, Efficiency, and Reimbursement. J Natl Compr Canc Netw 2011;9:S-1-S-16.
5. Korf BR, Rehm, HL. New Approaches to Molecular Diagnosis. JAMA. 2013;309(14);1511-1521.
6. Rutherford T, Orr J, et al. A prospective study evaluating the clinical relevance of a chemoresponse assay for treatment of patients with persistent or recurrent ovarian cancer. *Gynecol Onc.* 2013 Nov;131(2):362-7.
7. Aetna. Tumor Markers Clinical Policy Bulletin. Last Review: 08/25/17. Accessed 08/30/17. Retrieved from http://www.aetna.com/cpb/medical/data/300_399/0352.html
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Acute Myeloid Leukemia. Version 3.2017, 06/06/17. AML-1, AML-A. Accessed 11/27/17.
9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Anaplastic Gliomas/Glioblastoma. Version 1.2017, 08/18/2017. Accessed 11/27/17. GLIO-2
10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Central Nervous System Cancers. Version 1.2017, 08/18/2017. Accessed 11/27/17. BRAIN-D 1 of 6
11. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Invasive Breast Cancer. Version 3.2017, 11/10/17. Accessed 11/27/17. BINV-6
12. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL). Version 1.2018, 08/21/17. Accessed 08/30/17. CSLL-1
13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Chronic Myeloid Leukemia. Version 1.2018, 07/26/17. Accessed 08/30/17.

14. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Colon Cancer. Version 2.2017, 03/13/17. Accessed 08/30/17. MS-15, MS-16, COL-A 4 OF 5
15. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Colon Cancer. Version 2.2017, 03/13/17. Accessed 11/27/17. Discussion MS-3.
16. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Dermatofibrosarcoma Protuberans. Version 1.2018, 09/18/2017. Accessed 12/18/17. Discussion MS-3.
17. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Melanoma. Version 1.2018, 10/11/17. Accessed 11/28/17. ME-1 through ME-14, ME-A, ME-B, MS-5, MS-6
18. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Myelodysplastic Syndromes. Version 1.2018, 08/29/17. Accessed 11/27/17. MDS-2, MDS-7, MDS-C 1-4, MDS-D
19. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Hodgkin's Lymphomas. B-Cell Lymphomas. Version 7.2017, 12/05/17. Accessed 12/15/17. NHODG-A 2 of 11 and 6 of 11.
20. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Hodgkin's Lymphomas. Diffuse large B-Cell Lymphoma. Version 7.2017, 12/05/17. Accessed 12/15/17. BCEL-1
21. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Hodgkin's Lymphomas. Post-Transplant Lymphoproliferative Disorders. Version 7.2017, 12/05/17. Accessed 12/15/17. PTLD-1.
22. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Small Cell Lung Cancer. Version 8.2017, 07/14/17. Accessed 08/30/17. NCSL-17, NSCL-G 1-4, NSCL-H, NSCL-I 1 of 2
23. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Ovarian Cancer. Version 3.2017, 08/30/17. Accessed 08/30/17. MS-21 and MS-22
24. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Prostate Cancer Early Detection. Version 1.2017, 06/15/17. Accessed 12/05/17. PROSD-3, PROSD-4, MS-16- 22
25. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Thyroid Carcinoma. Version 2.2017, 05/17/2017. Accessed 08/30/17. MEDU-1

DOCUMENT HISTORY:

Created Date: 09/16/13
Reviewed Date: 09/16/14, 09/16/15, 05/26/16, 05/25/17
Revised Date: 06/17/14**,** 10/06/14, 12/30/14, 3/23/15, 05/26/16, 09/14/16, 08/30/17, 11/27/17, 01/16/18

Attachment A

Molecular Test	Condition	Indication
*1p19q codeletion CPT 88377 A, NCCN	Astrocytoma Glioma	Medically necessary for diagnosis and management.
4Kscore (free and total PSA [fPSA and tPSA], human kallikrein 2 [hK2], intact PSA, age, DRE results, and prior biopsy status) CPT 81539 NCCN	Prostate cancer detection	Medically necessary to further define the probability of high-grade cancer in members who have never undergone a biopsy or after a negative biopsy
5- hydroxyindolacetic acid (5-HIAA) CPT 83497 A	Neuroendocrine tumors	Medically necessary for diagnosis of neuroendocrine tumors
AFP (alpha-fetoprotein) CPT 82105 A	Hepatocellular cancer (HCC) Hepatocellular cancer in hepatitis B carriers Cirrhosis w/ risk factors: o Alcohol use o Alpha-antitrypsin deficiency o Asian female at least 50 years of age o Asian male at least 40 years of age o Family history of HCC o Genetic hemochromatosis o Hepatitis C o Nonalcoholic steatohepatitis o Stage 4 primary biliary cirrhosis Germ cell tumors in patients with adenocarcinoma, or carcinoma not otherwise specified, involving mediastinal nodes Mediastinal mass Ovarian cancer Pelvic mass Testicular cancer Testicular mass Thymic carcinoma Thymoma	Medically necessary for diagnosis and management.
* ALK gene fusion/ rearrangement (EML4[echinoderm microtubule-associated protein-like 4] -ALK [anaplastic lymphoma kinase)]) CPT 88271x2, 88274 A, NCCN	Diffuse large B cell lymphoma, Peripheral T-cell lymphoma, Post-transplant proliferative disorder Lung cancer including non-small cell lung cancer (NSCLC)	Medically necessary for diagnosis and management.

PreferredOne®

Department of Origin: Integrated Healthcare Services	**Approved by:** Howard K. Gold Chief Medical Officer	**Date Approved:** 12/19/17
Department(s) Affected: Claims, Coding, Customer Service, Integrated Healthcare Services	**Effective Date:** 01/03/18	
Medical Policy Document: Molecular Testing: Tumor/Neoplasm Biomarkers	**Replaces Effective Policy Dated:** 01/03/18	
Reference #: MP/M001	**Page:** 8 of 18	

Molecular Test	Condition	Indication
*BCR/ABL1 CPTs 81206, 81207, 81208 A, NCCN	Acute lymphocytic leukemia (ALL) Acute myeloid leukemia (AML) Chronic myelogenous leukemia (CML) Lymphoblastic lymphoma	>Medically necessary to determine if Ph+ (Philadelphia chromosome positive) ALL or AML >Medically necessary for the detection of resistance to imatinib mesylate (Gleevec), dasatinib (Sprycel) or nilotinib (Tasigna) for an individual with CML or Ph+ ALL or AML >Medically necessary for any of the following indications: o inadequate initial response to tyrosine kinase inhibitor therapy (ie, failure to achieve complete hematological response at 3 months, minimal cytogenetic response at 6 months or major cytogenetic response at 12 months) o loss of response to tyrosine kinase inhibitor therapy (ie, hematologic relapse, cytogenetic relapse, loss of major molecular response [MMR]) o progression to accelerated or blast phase CML while on tyrosine kinase inhibitor (TKI) therapy >Medically necessary to determine if bosutinib (BOSULIF) is a treatment option adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy. >Medically necessary as a diagnostic tool in lymphoblastic lymphoma and to determine eligibility for tyrosine kinase inhibitor therapy
Beta β-HCG CPT 84704 A	Mediastinal mass Ovarian cancer Pelvic mass Testicular mass / cancer Thyoma Thymic carcinoma	Medically necessary for diagnosis and management
Beta-2 β-2 (B2M) microglobulin CPT 82232 A	Multiple myeloma Non-Hodgkin's lymphoma Waldenstrom's Macroglobulinemia/Lymphoplasmacytic lymphoma	Medically necessary for diagnosis and management
*BRAF (v-raf murine sarcoma viral oncogene homolog B1) CPT 81210 A, NCCN	Lung cancer including non-small cell lung cancer (NSCLC) Melanoma	Medically necessary for diagnosis and management

Molecular Test	Condition	Indication
*BRAF V600 E CPT 81210 A, NCCN	Colorectal cancer /Lynch syndrome Gastrointestinal stromal tumors (GIST) Hairy cell leukemia Indeterminate thyroid nodule Melanoma Small bowel adenocarcinoma	Medically necessary for diagnosis and management.
CA 15-3, CA 27-29, or Truquant RIA CPT 86300 A	Metastatic breast cancer	Serial measurements of CA 15-3 (also known as CA 27-29 or Truquant RIA) is medically necessary for surveillance
CA 19-9 CPT 86301 A	Adenocarcinoma of the ampulla of Vater Gastric cancer Gallbladder cancer Cholangiocarcinoma Jaundice/abnl LFT Mucinous appendiceal carcinoma Pancreatic cancer	Medically necessary to monitor the clinical response to therapy or detect early recurrence of disease in patients with gastric cancer, pancreatic cancer, gallbladder cancer, cholangiocarcinoma or adenocarcinoma of the ampulla of Vater Medically necessary to rule out cholangiocarcinoma in persons with primary sclerosing cholangitis undergoing liver transplantation Medically necessary for evaluation of jaundice/abnl LFT Medically necessary as a tumor marker for mucinous appendiceal carcinoma Medically necessary to detect pancreatic cancer
CA 125 CPT 86304 A	Adenocarcinoma of unknown primary Epithelial ovarian cancer Endometrial cancer Ovarian mass Undiagnosed pelvic mass	Medically necessary for treatment monitoring and follow-up of epithelial ovarian cancer, endometrial cancer, adenocarcinomas of unknown primary, and undiagnosed suspicious pelvic masses
CALB2 (calretinin) CPT 88342 A	Lung cancer Occult primary	Medically necessary for diagnosis
CALCA (calcitonin) CPT 82308 A	Adenocarcinoma/anaplastic/undifferentiated tumors of head and neck Medullary thyroid cancer	Medically necessary for diagnosis
CD 20 (cluster of differentiation) CPT 88184 A	N/A	Medically necessary to determine eligibility for rituximab treatment

Molecular Test	Condition	Indication
CD 25 CPT 88184 A	N/A	Medically necessary to determine eligibility for denileukin diftitox treatment
CD 31 CPT 88342 A	Angiosarcoma	Medically necessary for diagnosis of angiosarcoma
CD 33 CPT 88184 A	N/A	Medically necessary to determine eligibility for anti-CD33 (gemtuzumab) treatment
CD 52 CPT 88184 A	N/A	Medically necessary to determine eligibility for anti-CD52 (alemtuzumab) treatment
*CD 117 (c-kit, KIT [v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene]) CPT 81272, 81273 A	N/A	Medically necessary to determine eligibility for anti-CD52 (imatinib mesylate) treatment
CEA (carcinoembryonic antigen) CPT 82378 A, NCCN	Colorectal cancer Cholangiocarcinoma Gallbladder cancer Lung cancer including non-small cell lung cancer (NSCLC) Medullary thyroid cancer Metastatic breast cancer Mucinous appendiceal carcinoma Mucinous ovarian cancer Pancreatic cyst Occult primary cancer Jaundice, abnl LFT	As a preoperative prognostic indicator in colorectal carcinoma or mucinous appendiceal carcinoma; or Pancreatic cyst fluid CEA for distinguishing mucinous from non-mucinous malignant pancreatic cysts; or To detect asymptomatic recurrence of colorectal cancer after surgical and/or medical treatment for the diagnosis of colorectal cancer; or To monitor response to treatment for metastatic colorectal cancer.
*CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) mutation CPT 81218 A, NCCN	Acute myeloid/myelogenous leukemia	Medically necessary to diagnose acute myeloid leukemia (also called acute myelogenous leukemia, acute nonlymphocytic leukemia, or ANLL)
*Chemotherapy/ Chemosensitivity/ Tumor Resistance Assay Testing (live tumor culture), such as but not limited to, ChemoFX Assay CPT 81479 NCCN	Recurrent ovarian cancer	Is considered investigative except for use in recurrent ovarian cancer disease with two or less previous chemotherapy regimens, and re-biopsy of tissue

Molecular Test	Condition	Indication
CHGA (chromagranin A) CPT 88316 A	Merkel Cell carcinoma Neuroendocrine tumors Non-Small Cell lung carcinoma (NSCLC) Occult primary	Medically necessary for diagnosis and management.
*Cyclin D1/ CCND1 CPT 81401 A	Mantle cell lymphoma	Medically necessary for the diagnosis and prediction of disease recurrence of mantle cell lymphoma
* EGFR (epidermal growth factor receptor) CPT 81235 A, NCCN	Lung cancer including non-small cell lung cancer (NSCLC)	Medically necessary as a molecular biomarker for lung cancer/NSCLC
ER/PR (estrogen receptors and progesterone receptors) CPTs 84233, 84234 A	Breast cancer	Medically necessary for primary and metastatic breast cancers as part of the general work-up and treatment planning
* FLT3-ITD (fms-related tyrosine kinase 3 internal tandem duplication) CPTs 81245, 81246 A, NCCN	Acute myeloid/myelogenous leukemia	Medically necessary to diagnose acute myeloid leukemia (also called acute myelogenous leukemia, acute nonlymphocytic leukemia, or ANLL) and to determine risk status for relapse
*Gene hypermethylation of GSTP1, APC, and RASSF1 genes (ConfirmMDx) CPT 81551 NCCN	Prostate cancer, suspect	Medically necessary for members thought to be at high risk of prostate cancer, despite a negative biopsy
HCG (human chorionic gonadotropin) CPT 84702, 84703, 84704 A	Carcinoma not otherwise specified (NOS) Embryonal cell carcinoma Germ cell tumors Teratocarcinoma Trophoblastic ovarian cancer Trophoblastic testicular cancer	Medically necessary to assist in the diagnosis of trophoblastic testicular cancer and trophoblastic ovarian cancer Medically necessary to diagnose or monitor germ cell tumors (teratocarcinoma and embryonal cell carcinoma) of the ovaries or testes; or patients with adenocarcinoma, or carcinoma not otherwise specified, involving mediastinal nodes
HER2 (human epidermal growth factor receptor 2) CPTs 83950, 88360, 88361 A, NCCN	Breast cancer Gastric cancer Esophageal cancer Lung cancer including non-small cell lung cancer (NSCLC)	Medically necessary in breast, gastric, esophageal and NSCL cancer to determine eligibility for biologic response modifying medications

Molecular Test	Condition	Indication
*IDH1 and IDH2 (isocitrate dehydrogenase) mutation CPT 83570 A	Acute myeloid/myelogenous leukemia (AML) Astrocytoma Chondrosarcoma Glioma	Medically necessary for the diagnosis and prognosis of AML, astrocytomas, chondrosarcomas and gliomas
*IGH@ (immunoglobulin heavy chain locus) rearrangement CPTs 81261 A	Non-Hodgkin's lymphoma Hairy cell leukemia Post-transplant lymphoproliferative disorder	Medically necessary to detect abnormal clonal population(s) in non-Hodgkin's lymphomas, hairy cell leukemia, and post-transplant lymphoproliferative disorder
*IGK@ immunoglobulin kappa light chain locus) rearrangement CPT 81264 A	Non-Hodgkin's lymphoma Systemic light chain amyloidosis	Medically necessary to detect abnormal clonal population(s) for non-Hodgkin's lymphoma, systemic light chain amyloidosis
ImmunoCyte / uCyt (fluorescence immunocytology CPT 88342 A	Bladder cancer	Medically necessary as an adjunct to cystoscopy or cytology in monitoring members with bladder cancer.
INHA (inhibin) CPT 86336 A	Ovarian cancer Pelvic mass	Medically necessary for diagnosis and management
*Janus Kinase 2 (JAK2) JAK2-V617F sequence variant CPT 81270 Janus Kinase 2 (JAK2) exon 12 sequence and exon 13 sequence CPT 81403 A	Chronic myeloproliferative disorders (CMPD) Polycythemia vera	Medically necessary for a qualitative assessment of JAK2-V617F sequence variant using methods with detection thresholds of up to 5% for initial diagnostic assessment of adult patients presenting with symptoms of CMPD Medically necessary for the diagnosis of polycythemia vera in adults Medically necessary to establish a differential diagnosis of essential thrombocytosis and primary myelofibrosis from reactive conditions in adults
* KIT (C-kit, CKIT) (CD-117 [cluster of differentiation-117]) CPT 81272, 81273 A, NCCN	Acute myeloid/myelogenous leukemia (AML) Gastrointestinal stromal tumors Melanoma	Medically necessary to diagnose acute myeloid leukemia (also called acute myelogenous leukemia, acute nonlymphocytic leukemia, or ANLL) and to determine risk status for relapse Medically necessary as a diagnostic tool for gastrointestinal stromal tumors (GIST) Medically necessary for diagnosis and management of melanoma

PreferredOne®

Department of Origin: Integrated Healthcare Services	**Approved by:** Howard K. Gold Chief Medical Officer	**Date Approved:** 12/19/17
Department(s) Affected: Claims, Coding, Customer Service, Integrated Healthcare Services	**Effective Date:** 01/03/18	
Medical Policy Document: Molecular Testing: Tumor/Neoplasm Biomarkers	**Replaces Effective Policy Dated:** 01/03/18	
Reference #: MP/M001	**Page:** 13 of 18	

Molecular Test	Condition	Indication
*KRAS (rat sarcoma) mutation analysis with BRAF reflex testing (see BRAF entry) CPT 81275, 81276 A	Anal adenocarcinoma Metastatic colorectal cancer Small bowel adenocarcinoma	Medically necessary to predict non-response to Erbitux (cetuximab) and Vectibix (panitumumab)
*KRAS (rat sarcoma) mutation CPT 81275, 81276 A	Lung cancer including non-small cell lung cancer (NSCLC)	Medically necessary to predict non-response to Tarceva (erlotinib)
LDH (lactate dehydrogenase) CPT 83615, 83625 A	Acute lymphoblastic leukemia (ALL) Bone cancer Kidney cancer or mass Lung cancer including non-small cell lung cancer (NSCLC) Multiple myeloma Non-Hodgkin's lymphoma Pelvic mass Ovarian cancer Testicular cancer or mass	Medically necessary for diagnosis and management.
*MMR (mismatch repair) /MLH1 (mutL homolog 1) or MSI (microsatellite instability), eg, MLH1, MSH2, MSH6 MSI CPT 81301 MMR/MLH1 CPT 81288, 81292, 81293, 81294 MSH2 CPT 81295, 81296, 81297 MSH6 CPT 81298, 81299, 81300 A, NCCN	Colorectal cancer	Medically necessary for all patients younger than 50 years of age with colorectal cancer (increased likelihood of Lynch syndrome) Medically necessary for all patients with stage II colorectal cancer.
MPO (myeloperoxidase) CPT 83876 A	Acute myeloid leukemia	Medically necessary to diagnose acute myeloid leukemia (also called acute myelogenous leukemia, acute nonlymphocytic leukemia, or ANLL)
*NPM1 (nucleophosmin) mutation CPT 81310 A, NCCN	Acute myeloid/myelogenous leukemia	Medically necessary to diagnose acute myeloid leukemia (also called acute myelogenous leukemia [AML], acute nonlymphocytic leukemia [ANLL] and determine risk of relapse

PreferredOne®

Department of Origin: Integrated Healthcare Services	**Approved by:** Howard K. Gold Chief Medical Officer	**Date Approved:** 12/19/17
Department(s) Affected: Claims, Coding, Customer Service, Integrated Healthcare Services	**Effective Date:** 01/03/18	
Medical Policy Document: Molecular Testing: Tumor/Neoplasm Biomarkers	**Replaces Effective Policy Dated:** 01/03/18	
Reference #: MP/M001	**Page:** 14 of 18	

Molecular Test	Condition	Indication
*NRAS (neuroblastoma RAS viral [v-ras] oncogene CPT 81311 NCCN	Colorectal cancer	NRAS testing is medically necessary for suspected or proven metastatic or synchronous adenocarcinoma (any T, any N, M1).
PAI-1 (plasminogen activator inhibitor 1) CPT 85415 A	Breast cancer	Medically necessary to where all of the following are met: • node-negative • ER+ , HER2-
PCA3 (DD3) (noncoding, prostate tissue-specific RNA) CPT 81313 NCCN	Prostate cancer detection	Medically necessary to further define the probability of high-grade cancer in members who have never undergone a biopsy or after a negative biopsy
PDGFRα (platelet-derived growth factor receptor, alpha polypeptide) CPT 81314 A	Gastrointestinal stromal tumors (GIST)	Medically necessary for diagnosis and treatment
PDGFRβ (platelet-derived growth factor receptor, beta polypeptide) No specific CPT code A, NCCN	Chronic myelomonocytic leukemia (CMML) Dermatofibrosarcoma protuberans Myelodysplastic syndromes (MDS)	Medically necessary for diagnosis and treatment
PD-L1 (programmed death ligand 1) No specific CPT code NCCN	Lung cancer including non-small cell lung cancer (NSCLC)	Medically necessary as a molecular biomarker for lung cancer/NSCLC
Percent free PSA CPT 84154 NCCN	Prostate cancer detection	Medically necessary to further define the probability of high-grade cancer in members who have never undergone a biopsy or after a negative biopsy
Placental alkaline phosphatase (PLAP) CPT 84040 A	Germ cell seminoma Non-seminoma germ cell tumors in unknown primary cancers	Medically necessary to diagnose germ cell seminoma and non-seminoma germ cell tumors in unknown primary cancers
*PML/RARA CPT 81315, 81316 A	Acute promyelocytic leukemia	Medically necessary to diagnose acute promyelocytic leukemia

PreferredOne®

Department of Origin: Integrated Healthcare Services	**Approved by:** Chief Medical Officer	**Date Approved:** 12/19/17
Department(s) Affected: Claims, Coding, Customer Service, Integrated Healthcare Services	**Effective Date:** 01/03/18	
Medical Policy Document: Molecular Testing: Tumor/Neoplasm Biomarkers	**Replaces Effective Policy Dated:** 01/03/18	
Reference #: MP/M001	**Page:** 15 of 18	

Molecular Test	Condition	Indication
PHI (Prostate Health Index [tPSA, fPSA, and proPSA]) No specific CPT code NCCN	Prostate cancer	Medically necessary to further define the probability of high-grade cancer in members who have never undergone a biopsy or after a negative biopsy
PSA (prostate-specific antigen) CPT 84152, 84153, 84154, G0103 A	Prostate cancer	Medically necessary the management of prostate cancer including staging, monitoring response to therapy, and detecting disease recurrence (A) risk stratification and predicting prognosis
*Proteomic testing, such as but not limited to, Veristrat, Xpresys Lung No specific CPT code A, NCCN	Lung cancer including non-small cell lung cancer (NSCLC)	Medically necessary for members with advanced NSCLC whose tumors were without EGFR and ALK mutations who have progressed after at least one chemotherapy regimen
*PTEN (phosphotase and tensin homolog) CPT 81321, 81322, 81323 A	Cowden Syndrome	Medically necessary for persons meeting Cowden syndrome testing (see MC/L010)
*ROS1 No specific CPT code A, NCCN	Lung cancer including non-small cell lung cancer (NSCLC)	Medically necessary as a molecular biomarker for lung cancer/NSCLC; predict response to Xalkori
*RUNX1 CPT 81334 A	Myelodysplastic syndrome	Medically necessary for diagnosis and management.
*T-cell receptor gene rearrangements (TRA@, TRB@, TRD@, TRG@) (previously TCB@ and TCG@) CPT TRA@ no specific CPT code, TRB@ 81340 or 81341, TRD@ 81402, TRG@ 81342 A	Castleman's disease Mycosis fungoides/ Sezary syndrome Nasal type extranodal NK/T-cell lymphoma Peripheral T-cell lymphoma Primary cutaneous CD30+ T-cell lymphoproliferative disorders T-cell prolymphocytic leukemia T-cell large granular lymphocytic leukemia	Medically necessary for diagnosis and management.

Molecular Test	Condition	Indication
*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 CPT 81445 A, NCCN	Lung cancer including non-small cell lung cancer (NSCLC) NCCN (eg, FoundationOne®, ResponseDX® Lung)	Medically necessary for diagnosis and management.
*Targeted genomic sequence analysis panel, solid organ or hematolymphoid 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 of mRNA expression levels, if performed CPT 81450 A, NCCN	Myelodysplastic syndromes - including but not limited to the following genes: TET2, DNMT3A, ASXL1, EZH2, SF3B1, SRSF2, U2AF1, ZRSR2, TP53, STAG2, NRAS, RUNX1, CBL, JAK2, SETBP1, IDH1, IDH2, ETV6	Medically necessary to establish presence of clonal hematopoiesis, to help exclude benign causes of cytopenias in cases with non-diagnostic morphology

PreferredOne®

Department of Origin: Integrated Healthcare Services	**Approved by:** Howard K. Gold Chief Medical Officer	**Date Approved:** 12/19/17
Department(s) Affected: Claims, Coding, Customer Service, Integrated Healthcare Services	**Effective Date:** 01/03/18	
Medical Policy Document: Molecular Testing: Tumor/Neoplasm Biomarkers	**Replaces Effective Policy Dated:** 01/03/18	
Reference #: MP/M001	**Page:** 17 of 18	

Molecular Test	Condition	Indication
*Targeted genomic sequence analysis panel, solid organ or hematolymphoid disorder, 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 CPT 81455 NCCN	Myelodysplastic syndromes	Medically necessary to establish presence of clonal hematopoiesis, to help exclude benign causes of cytopenias in cases with non-diagnostic morphology
*Thymidine kinase CPT 81405 A	Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)	Medically necessary for diagnosis and management.
Thyroglobulin antibodies CPT 86800 A	Thyroid cancer	Medically necessary for diagnosis and management.
Thyroglobulin TG expression CPT 84432 A	Adenocarcinoma or anaplastic/ undifferentiated tumors of the head and neck Occult primary Thyroid cancer	Medically necessary for diagnosis and management.
* Thyroid fine needle aspiration (FNA) analysis, eg, Afirma, Quest Diagnostics Thyroid Cancer Mutation Panel, ThyGenX, ThyroSeq CPT 81545 A, NCCN	Cytologically indeterminate thyroid nodule	Medically necessary for cytologically indeterminate thyroid nodules. Oncogenes typically include BRAF, PAX8/PPAR, RAS (HRAS, KRAS, NRAS) RET/PTC.

PreferredOne®

Department of Origin: Integrated Healthcare Services	**Approved by:** Chief Medical Officer	**Date Approved:** 12/19/17
Department(s) Affected: Claims, Coding, Customer Service, Integrated Healthcare Services	**Effective Date:** 01/03/18	
Medical Policy Document: Molecular Testing: Tumor/Neoplasm Biomarkers	**Replaces Effective Policy Dated:** 01/03/18	
Reference #: MP/M001	**Page:** 18 of 18	

Molecular Test	Condition	Indication
* Thyroid fine needle aspiration (FNA) analysis, ThyraMIR CPT 0018U A	Cytologically indeterminate thyroid nodule	Medically necessary for cytologically indeterminate thyroid nodules as a reflex test following ThyGenX
Thyroid transcription factor (TTF-1) No specific CPT code A	Lung cancer including non-small cell lung cancer (NSCLC) Neuroendocrine tumors	Medically necessary for diagnosis and management.
*TP53 (tumor protein 53) CPTs 81404, 81405 NCCN	Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)	Medically necessary to determine prognosis and/or therapy.
*uPA (urokinase plasminogen activator) CPT 85415 A	Breast cancer	Medically necessary where all of the following are met: • node-negative • ER+, HER2-
*Urinary biomarkers, eg, bladder tumor antigen (BTA [BTA Stat, BTA TRAK]); Nuclear matrix protein (NMP220; fibrin/fibrinogen degradation products (Aura-Tek FDfP); or UroVysion™ No specific CPT code A	Bladder cancer	Medically necessary for follow-up of treatment for bladder cancer; or Monitoring for eradication of bladder cancer; or Recurrences after eradication
WT-1 gene expression No specific CPT code A	Lung cancer including non-small cell lung cancer (NSCLC) Occult primary	Medical necessary for diagnosis
ZAP-70 (zeta-chain-associated protein kinase 70) CPT 88184, 88185 A	Chronic lymphocytic leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)	Medically necessary for assessing prognosis and need for aggressive therapy

A: Aetna
NCCN: National Comprehensive Cancer Network

Revised 11/27/17