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

PURPOSE:
The purpose of this policy is to provide coverage guidelines for molecular based tumor marker testing on tissue, bone marrow 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) Biomarkers Compendium® positions for requests for these services.

COVERAGE:
I. General characteristics of covered tests
   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.

II. Request for use of gene-expression profiling meets MC/L012 Gene Expression Profiling.
III. Requests for molecular tumor/neoplasm biomarker testing is appropriate per the National Comprehensive Cancer Network (NCCN) Biomarkers Compendium® Guideline or Disease for the member’s condition, based on both of the following:

A. The member’s diagnosis matches the Disease Description field; and

B. The provider has ordered the molecular tumor/neoplasm biomarker after following the appropriate sequence of testing described in the NCCN Recommendation: Clinical Decision field, when indicated.

IV. Requests for simultaneous testing of multiple markers through targeted genomic next generation sequencing (NGS) panels of 5-50 genes (CPTs 81445, 81450) are covered when supported by NCCN Biomarkers Compendium® - any of the following: A-E

A. Lung cancer including non-small cell lung cancer (NSCLC) (tumor/tissue, eg, FoundationOne® ResponseDX® Lung, Oncomine DX Target Test [CPT 81445]); or

B. Myelodysplastic and myeloproliferative syndromes (blood or bone marrow aspirate [CPT 81450]); or

C. Colon cancer (CPT 81445); or

D. Acute lymphoblastic leukemia (CPT 81450); or

E. Other disease that includes a recommendation for NGS/sequencing testing.

EXCLUSIONS:
Either of the following: I or II

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

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):
   1. 41-gene signature assay
   2. BluePrint® (80-gene profile)
   3. Breast Cancer Gene Expression Ratio (also known as Theros H/ISM [HCPCS S3854])
   4. BreastNextTM
   5. BreastOnePx™ or Breast Cancer Prognosis Gene Expression Assay
   6. BreastPRS
   7. Genomic Grade Index (also known as MapQuant Dxtm)
   8. HERmark® Breast Cancer Assay
   9. Insight™ DX Breast Cancer Profile
   10. Mammostrat™
   11. NexCourse® Breast IHC4
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12. Oncotype DX® DCIS (PLA 0045U)
13. SYMPHONY™ Genomic Breast Cancer Profile
14. TargetPrint®

**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):
1. CancerTYPE ID® Test (CPT 81540)
2. ProOnc TumorSourceDX™ Test CPT 81540)
4. Rosetta Cancer Origin Test™ (miRview® mets and miRview® mets2 tests) CPT 81540)

**E.** Gene expression profiling/molecular testing for colorectal cancer, such as, but not limited to all of the following (see Investigative List):
1. ColDx
2. ColoPrint
3. Colorectal Cancer DSA®
4. GeneFx Colon®
5. OncoDefender-CRC®
6. Oncotype DX® Colon Cancer Assay
7. Polyp DX (PLA 0002U)

**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):
1. OVA1 (CPT 81503, PLA 0003U)
2. Risk of Ovarian Malignancy Algorithm (ROMA [CPT 81500])

**G.** Gene expression profiling/molecular testing for prostate cancer, such as, but not limited to the following (see Investigative List):
1. TMPRSS:ERG (Transmembrane protease, serine: ERG [ETS related gene] fusion genes for diagnosis and prognosis of prostate cancer (eg, ProstaVysion®))
2. ExomeDX Prostate (PLA 0005U)
3. Apfinity (PLA 0021U)
4. Prostate Cancer Risk Panel – Mayo (PLA 0053U)
5. NeoLAB Prostate liquid biopsy (CPT 0011M)

**H.** Gene expression profiling/molecular testing for cutaneous melanoma, such as but not limited to, Decision DX-Melanoma (see Investigative List)
[Note: does not apply to uveal melanoma testing with Decision DX-UM]

**I.** Circulating tumor cells/markers or cell-free tumor DNA testing for the management of all cancers, specifically breast, colorectal, melanoma, and prostate (see Investigative List): Examples include, but are not limited to, CancerIntercept® Detect (liquid biopsy), CellSearch® System, FoundationOne® ACT (liquid biopsy), GeneStrat (liquid biopsy), Guardant 360® (CPT 86152)

**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 (e.g., 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.
FOR INTERNAL USE ONLY

COVERAGE:
Prior Authorization: Yes

Coverage is subject to the member’s contract benefits.

CODING:
CPTs
81445 Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed. Can allow for NSCLC.

81450 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 isofom expression of mRNA expression levels, if performed. Can allow for myelodysplastic or myeloproliferative disorders.

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RELATED CRITERIA/POLICIES:
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
Medical Criteria: MC/L012 Gene Expression Profiling

REFERENCES

DOCUMENT HISTORY:

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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, 05/17/19
PreferredOne Community Health Plan Nondiscrimination Notice

PreferredOne Community Health Plan ("PCHP") complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. PCHP does not exclude people or treat them differently because of race, color, national origin, age, disability, or sex.

PCHP:
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)


Language Assistance Services

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).


注意：如果您使用繁體中文，您可以免費獲得語音援助服務，請致電 1.800.940.5049 (TTY: 763.847.4013).

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 1.800.940.5049 (телетайп: 763.847.4013).

โปรดติดต่อทีมผู้ให้บริการด้านการสื่อสารที่มีการสนับสนุนอื่น ๆ โดยใช้ภาษาอื่น ๆ ที่สามารถเข้าถึงได้จากในประเทศ โทร 1.800.940.5049 (TTY: 763.847.4013).


주의: 한국어로 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 1.800.940.5049 (TTY: 763.847.4013).
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• 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

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U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
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In tümleşik: "Sizce i̇ngilizce konuşmayorsanız, ücretsiz destek hizmetleri bulunmaktadır. 1.800.940.5049 (TTY: 763.847.4013)."

МЕНИГЭ: Эсэхийн нэг нь англи түвшнээс бүх мэргэжил хэлэнд нийтэлбээс нэг нь даруй суурийн түвшин товчлолтой. 1.800.940.5049 (TTY: 763.847.4013).


ПРИМЕЧАНИЕ: Если вы говорите по-русски, вам предоставляются бесплатные переводные услуги по телефону 1.800.940.5049 (TTY: 763.847.4013).

ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1.800.940.5049 (TTY: 763.847.4013).

주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 1.800.940.5049 (TTY: 763.847.4013), 번으로 전화해 주십시오.

PAUNAWA: Kung nagsasalita ka ng Tagalog, maara kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 1.800.940.5049 (TTY: 763.847.4013).