

MEDICAL POLICY

POLICY TITLE	GENE EXPRESSION BASED ASSAYS FOR CANCERS OF UNKNOWN PRIMARY
POLICY NUMBER	2.245

Effective Date:	9/1/2023
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I. POLICY

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Gene expression profiling is considered **investigational** to evaluate the site of origin of a tumor of unknown primary and to distinguish a primary from a metastatic tumor. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

Policy Guidelines

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-reference:

MP 2.326 General Approach to Genetic Testing

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

III. DESCRIPTION/BACKGROUND

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Cancers of Unknown Primary

Cancers of unknown primary (CUPs), or occult primary malignancies, are tumors that have metastasized from an unknown primary source; they make up approximately 3% of all cancers in the United States.

Most CUPs are adenocarcinomas or undifferentiated tumors; less commonly, they may be squamous carcinomas, melanoma, soft tissue sarcoma, or neuroendocrine tumors. Osteo- and

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chondrosarcomas rarely produce CUPs. The most common primary sites of CUPs are lung and pancreas, followed by colon and stomach, then breast, ovary, prostate, and solid-organ carcinomas of the kidney, thyroid, and liver. Conventional methods used to aid in the identification of the origin of a CUP include a thorough history and physical examination; computed tomography scans of the chest, abdomen, and pelvis; routine laboratory studies; and targeted evaluation of specific signs and symptoms.

Diagnosis and Classification

Cancers of unknown primary can be classified into 4 categories. Adenocarcinomas compose approximately 70% of cancers of unknown primary. Neuroendocrine tumors compose approximately 1%, squamous cell carcinomas 5%, and poorly differentiated cancer 20% to 25% of cancers of unknown primary.

Biopsy of a CUP with detailed pathology evaluation may include immunohistochemical (IHC) analysis of the tumor. IHC identifies different antigens present on different types of tumors and can usually distinguish an epithelial tumor (i.e., carcinoma) from melanoma or sarcoma. Detailed cytokeratin panels often allow further classification of carcinoma; however, tumors of different origins may show overlapping cytokeratin expression. Results of IHC may provide a narrow differential of possible sources of a tumor’s origin, but not necessarily a definitive answer.

Treatment Selection and Health Outcomes

Treatment is based on the histologic type and clinical features. About 20% of patients with cancer of unknown primary have features that guide treatment. However, about 80% of patients with cancer of unknown primary have a poor prognosis with a survival of 3–6 months despite a variety of chemotherapeutic combinations. Multiple sites of involvement are observed in about 50% of patients, commonly in the lungs, liver, bones, and lymph nodes. The premise of tissue of origin testing in cancers of unknown primary is that identifying a likely primary tumor site will inform treatment selection leading to improved survival and other outcomes.

Tests Reviewed in This Report

Selected gene expression profiling tests are described in Table 1.

Table 1. Gene Expression Profiling Tests for CUP

Test	Manufacturer	Platform	Genes Assayed, n	Tumor Types Assessed, n
Tissue of Origin^a	Cancer Genetics	Oligonucleotide microarray	2000	15
CancerTYPE ID	Biotheranostics	RT-qPCR	92	54

Adapted from Agwa et al (2013)

RT-qPCR: real-time quantitative polymerase chain reaction.

^a Formerly PathWork® and ResponseDX: Tissue of Origin

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Regulatory Status

In 2008, the PathWork® Tissue of Origin Test™ (Response Genetics; now Cancer Genetics, Cancer Genetics merged with StemoniX in 2020.) was cleared for marketing with limitations (see below) by the U.S. Food and Drug Administration (FDA) through the 510(k) process (FDA product code: OIW), with subsequent clearances for expanded applications in 2010 and minor modifications in 2012. FDA determined that the test was substantially equivalent to existing tests for use in measuring the degree of similarity between the RNA expression pattern in a patient's fresh-frozen tumor and the RNA expression patterns in a database of tumor samples (poorly differentiated, undifferentiated, metastatic cases) that were diagnosed according to current clinical and histopathologic practice.

Limitations to the clearance were as follows:

- The PathWork® Tissue of Origin Test is not intended to establish the origin of tumors that cannot be diagnosed according to current clinical and pathologic practice (eg, a cancer of unknown primary).
- It is not intended to subclassify or modify the classification of tumors that can be diagnosed by current clinical and pathologic practice or to predict disease course, or survival or treatment efficacy, or to distinguish primary from metastatic tumor.
- Tumor types not in the PathWork® Tissue of Origin Test database may have RNA expression patterns similar to RNA expression patterns in tumor types in the database, leading to indeterminate results or misclassifications.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). CancerTYPE ID® (Biotheranostics, San Diego, CA) is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

IV. RATIONALE

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Summary of Evidence

For individuals who have cancers of unknown primary who receive gene expression profiling, the evidence includes studies of clinical validity, and 2 randomized controlled trials (RCTs) that have evaluated clinical utility. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. Of the 2 commercially available tests reviewed, one has been cleared by the U.S. Food and Drug Administration (Tissue of Origin). For these tests, the clinical validity is the ability of a test to determine the site of origin. Using different reference standards (known tumor type, reference diagnosis, a primary tumor identified during follow-up, immunohistochemical analysis) for the tissue of origin, the tests have reported sensitivities or concordances generally high (e.g., 80% to 90% or more). However, the reference standard is imperfect, and evidence for clinical validity does not support potential benefit. Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with and without the test. The benefit would be most convincingly demonstrated through a trial randomizing patients with cancers of unknown primary to receive treatment based on gene expression profiling results or usual care. One published RCT and one conference presentation

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with this design were identified. These trials did not find a survival benefit for patients with cancers of unknown primary who received treatment based on the site of origin as determined by molecular testing. A limitation in interpretation of the published trial results is that there were few treatments that were site specific, so there was minimal difference in the actual treatments given to the two groups. In the second RCT, most cancers responded to the control treatments. Therefore, the possibility remains that if more site-specific treatments are developed, molecular testing to determine the site of origin in patients with cancers of unknown primary may have clinical utility, but the absence of convincing evidence from RCTs prevents conclusions about clinical utility. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome

V. DEFINITIONS

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VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice, and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

The following codes are investigational when used to report gene expression testing for cancer of unknown primary as outlined in the policy statement:

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Procedure Codes							
81479	81504	81540	81599		8		

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1. PDQ Adult Treatment Editorial Board. Carcinoma of Unknown Primary Treatment (PDQ). 2018
2. Oien KA, Evans TR. Raising the profile of cancer of unknown primary. *J Clin Oncol.* Sep 20 2008; 26(27):4373- 4375. PMID 18802148
3. Ma XJ, Patel R, Wang X, et al. Molecular classification of human cancers using a 92-gene real-time quantitative polymerase chain reaction assay. *Arch Pathol Lab Med.* Apr 2006; 130(4):465-473. PMID 16594740
4. Ramaswamy S, Tamayo P, Rifkin R, et al. Multiclass cancer diagnosis using tumor gene expression signatures. *Proc Natl Acad Sci U S A.* Dec 18, 2001; 98(26):15149-15154. PMID 11742071
5. Su AI, Welsh JB, Sapinoso LM, et al. Molecular classification of human carcinomas by use of gene expression signatures. *Cancer Res.* Oct 15 2001; 61(20):7388-7393. PMID 11606367
6. Tothill RW, Kowalczyk A, Rischin D, et al. An expression-based site of origin diagnostic method designed for clinical application to cancer of unknown origin. *Cancer Res.* May 15 2005; 65(10):4031-4040. PMID 15899792
7. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: occult primary (cancer of unknown primary [CUP]). Version 3.2023
8. Agwa E, Ma PC. Overview of various techniques/platforms with critical evaluation of each. *Curr Treat Options Oncol.* Dec 2013; 14(4):623-633. PMID 24243164
9. U.S. Food and Drug Administration. 510(k) Substantial Equivalence Determination Decision Summary: Pathwork Tissue of Origin Test. 2008
10. U.S. Food and Drug Administration. 510(k) Substantial Equivalence Determination Decision Summary: Pathwork Tissue of Origin Test Kit-FFPE. 2010
11. Monzon FA, Lyons-Weiler M, Buturovic LJ, et al. Multicenter validation of a 1,550-gene expression profile for identification of tumor tissue of origin. *J Clin Oncol.* May 20 2009; 27(15):2503-2508. PMID 19332734
12. Azueta A, Maiques O, Velasco A, et al. Gene expression microarray-based assay to determine tumor site of origin in a series of metastatic tumors to the ovary and peritoneal carcinomatosis of suspected gynecologic origin. *Hum Pathol.* Jan 2013; 44(1):20-28. PMID 22939961
13. Handorf CR, Kulkarni A, Grenert JP, et al. A multicenter study directly comparing the diagnostic accuracy of gene expression profiling and immunohistochemistry for primary site identification in metastatic tumors. *Am J Surg Pathol.* Jul 2013; 37(7):1067-1075. PMID 23648464
14. Erlander MG, Ma XJ, Kesty NC, et al. Performance and clinical evaluation of the 92-gene real-time PCR assay for tumor classification. *J Mol Diagn.* Sep 2011; 13(5):493-503. PMID 21708287
15. Kerr SE, Schnabel CA, Sullivan PS, et al. Multisite validation study to determine performance characteristics of a 92-gene molecular cancer classifier. *Clin Cancer Res.* Jul 15 2012; 18(14):3952-3960. PMID 22648269

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16. Kerr SE, Schnabel CA, Sullivan PS, et al. A 92-gene cancer classifier predicts the site of origin for neuroendocrine tumors. *Mod Pathol.* Jan 2014; 27(1):44-54. PMID 23846576
17. Brachtel EF, Operana TN, Sullivan PS, et al. Molecular classification of cancer with the 92-gene assay in cytology and limited tissue samples. *Oncotarget.* May 10 2016; 7(19):27220-27231. PMID 27034010
18. Greco FA, Lennington WJ, Spigel DR, et al. Molecular profiling diagnosis in unknown primary cancer: accuracy and ability to complement standard pathology. *J Natl Cancer Inst.* Jun 5 2013; 105(11):782-790. PMID 23641043
19. Greco FA, Lennington WJ, Spigel DR, et al. Poorly differentiated neoplasms of unknown primary site: diagnostic usefulness of a molecular cancer classifier assay. *Mol Diagn Ther.* Apr 2015; 19(2):91-97. PMID 25758902
20. Hayashi H, Kurata T, Takiguchi Y et al. Randomized Phase II Trial Comparing Site-Specific Treatment Based on Gene Expression Profiling With Carboplatin and Paclitaxel for Patients With Cancer of Unknown Primary Site. *J. Clin. Oncol.* 2019 Mar; 37(7). PMID 30653423
21. Fizazi, K, Maillard, A. Penel, N. et al. A phase 3 trial of empiric chemotherapy with cisplatin and gemcitabine or systemic treatment tailored by molecular gene expression in patient with carcinomas of an unknown primary site (GEFCAPI 04). *ESMO Congress presentation.* 2019.
22. Nystrom SJ, Hornberger JC, Varadhachary GR, et al. Clinical utility of gene-expression profiling for tumor-site origin in patients with metastatic or poorly differentiated cancer: impact on diagnosis, treatment, and survival. *Oncotarget.* Jun 2012; 3(6):620-628. PMID 22689213
23. Yoon HH, Foster NR, Meyers JP, et al. Gene expression profiling identifies responsive patients with cancer of unknown primary treated with carboplatin, paclitaxel, and everolimus: NCCTG N0871 (alliance). *Ann Oncol.* Feb 2016; 27(2):339-344. PMID 26578722
24. Hainsworth JD, Schnabel CA, Erlander MG, et al. A retrospective study of treatment outcomes in patients with carcinoma of unknown primary site and a colorectal cancer molecular profile. *Clin Colorectal Cancer.* Jun 2012; 11(2):112-118. PMID 22000811
25. Hainsworth JD, Rubin MS, Spigel DR, et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon research Institute. *J Clin Oncol.* Jan 10 2013; 31(2):217-223. PMID 23032625
26. Prasad V, Oseran A, Fakhrejehani F. The use of gene expression profiling and mutation analysis increases the cost of care for patients with carcinoma of unknown primary; does it also improve survival? *Eur J Cancer.* Feb 2016; 54:159-162. PMID 26608119
27. National Institute for Health and Care Excellence (NICE). *Metastatic malignant disease of unknown primary origin in adults: diagnosis and management [CG104].* 2010.
28. Meleth S, Whitehead N, Evans TS, et al. *Genetic Testing or Molecular Pathology Testing of Cancers with Unknown Primary Site to Determine Origin.* AHRQ Technology Assessments. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
29. Medicare Evidence Development & Coverage Advisory Committee. *MEDCAC Meeting 5/1/2013 - Genetic Tests for Cancer Diagnosis.* 2013

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30. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.54 Gene Expression-Based Assays for Cancers of Unknown Primary. April 2023*

X. POLICY HISTORY

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MP-2.245	CAC 2/28/12 New policy adopting BCBSA. Information regarding the Pathwork® Tissue of Origin test is also addressed in the table in MP-2.212 Tumor Markers and Tumor Related Molecular Testing where it is listed as investigational.
	CAC 6/4/13 Consensus review. Other tests commercially available besides Pathwork were added to the policy. Policy statement changed to be generalizable to gene expression profiling and not specific to the Pathwork test. References updated. FEP variation revised to refer to the FEP manual. Medicare variation added referencing L33142 as this is a covered test for Medicare.
	04/08/13 Admin code review. Deleted codes removed from policy
	12/19/2013 New 2014 Code updates made.
	CAC 3/25/14 Consensus review. References updated. No changes to the policy statements. Rationale added for this review. No coding changes.
	7/24/14 Administrative change for the Medicare variation - For Novitas MAC jurisdictions, the LCD has been assigned a new number. Biomarkers for Oncology LCD changed from L33124 to L34796
	CAC 3/24/15 Consensus review. Policy title changed to Gene Expression-Based Assays for Cancers of Unknown Primary. Title changed to reflect range of gene expression test types. References and rationale updated. No changes to the policy statements. Codes reviewed.
	11/2/15 Administrative change. LCD number changed from L34796 to L35396 due to Novitas update to ICD-10.
	CAC 3/29/16 Consensus review. No change to the policy statement. Reference and rationale update. Coding reviewed; 2016 code added.
	Admin update 1/1/17: Product variation section reformatted.
	CAC 3/29/16 Consensus review. No change to the policy statement. Reference and rationale update. Coding updated to add 81479.
	10/1/17 Administrative Update: New codes added (0019U, 0021U, 0023U) with effective date 10/1/17.
	1/1/18 Admin Update: Medicare variations removed from Commercial Policies.
	1/16/18 Consensus review. No change to policy statements. References and rationale updated.
	1/16/19 Consensus review. No change to policy statements. References and rationale updated. Coding updated.
1/24/2020 Consensus review. No change to policy statements. References reviewed. Coding reviewed.	
5/20/2020 Administrative review. New code 0174U added to the policy. Product Variation, Benefit Variation, and Disclaimer updated.	

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	12/29/2020 Consensus review. No change to policy statement. Updated FEP Policy name under Product Variations. References updated. Coding reviewed. Added code 81599 to the policy.
	3/9/2021: Added NCCN statement.
	2/15/2022: Consensus review. No change to policy statement. Updated FEP and background. References and coding reviewed.
	6/1/2023 Consensus review. Cross references, background, and references. Updated coding table by deleting 0019U and 0174U from the policy.

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