

Medical Policy



Nonprofit corporations and independent licensees
of the Blue Cross and Blue Shield Association

Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 3/1/25**
(See policy history boxes for previous effective dates)

Title: Genetic Testing-Microarray Testing for Cancers of Unknown Primary (CUP) Origin

Description/Background

Cancers of unknown primary (CUP) represent 3% of all cancer cases in the U.S. A detailed history and physical, as well as radiologic and histologic testing can identify some but not all primary sources of secondary tumor.¹ It is suggested that identifying a likely primary source and directing treatment accordingly may improve health outcomes.

CANCERS OF UNKNOWN PRIMARY

Most CUPs are adenocarcinomas or undifferentiated tumors; less commonly, they may be squamous carcinomas, melanoma, soft tissue sarcoma, or neuroendocrine tumors. Osteo- and chondrosarcomas rarely produce cancers of unknown primary. The most common primary sites of cancers of unknown primary 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 (CT) scans of the chest, abdomen, and pelvis; routine laboratory studies; and targeted evaluation of specific signs and symptoms.²

Diagnosis and Classification

Cancers of unknown primary can be classified into 4 categories. Adenocarcinomas comprise approximately 70% of cancers of unknown primary. Neuroendocrine tumors comprise approximately 1%, squamous cell carcinomas 5% and poorly differentiated cancer 20 -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 a melanoma or sarcoma. Detailed cytokeratin panels often allow further classification of a carcinoma; however, tumors of different origins may show overlapping cytokeratin expression. The 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 CUP have a poor prognosis with a median survival of 3 to 10 months.⁷ 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 CUPs 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 CUP⁸

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

CUP: cancer of unknown primary; RT-qPCR: real-time quantitative polymerase chain reaction.

^a Formerly PathWork® and ResponseDX: Tissue of Origin™.

Regulatory Status

In July 2008, test “Pathwork® Tissue of Origin” (Pathwork Diagnostics, Inc., Sunnyvale, CA) was cleared with limitations* for marketing by the U.S Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that the test was 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, and metastatic cases) that were diagnosed according to current clinical and pathologic practice. The database contains examples of RNA expression patterns for 15 common malignant tumor types: bladder, breast, colorectal, gastric, hepatocellular, kidney, non-small cell lung, ovarian, pancreatic, prostate, and thyroid carcinomas, melanoma, testicular germ cell tumor, non-Hodgkin's lymphoma (not otherwise specified), and soft tissue sarcoma (not otherwise specified).

The Pathwork® Tissue of Origin Test result is intended for use in the context of the patient's clinical history and other diagnostic tests evaluated by a qualified clinician.

*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, (e.g., carcinoma 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, nor to predict disease course, survival, 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 that are similar to RNA expression patterns in tumor types in the database, leading to indeterminate results or misclassifications.

In June 2010, the “Pathwork® Tissue of Origin Test Kit-FFPE” (Pathwork Diagnostics) was cleared for marketing by the FDA through the 510(k) process. The 2010 clearance is an expanded application, which allows the test to be run on a patient’s formalin-fixed, paraffin-embedded (FFPE) tumor and has the same indications and limitations. In May 2012, minor modifications to the “Pathwork® Tissue of Origin Test Kit-FFPE” were determined to be equivalent to the previously approved device by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The test is now offered by Cancer Genetics, as the Tissue of Origin® test.

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. CancerTYPE ID® (Biotheranostics, San Diego, CA) is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Medical Policy Statement

Microarray genetic testing is considered **experimental/investigational** to identify the origin of a cancer of unknown primary, or to distinguish a primary from a metastatic tumor. The peer reviewed medical literature has not yet shown that the test has sufficient diagnostic accuracy to provide clinically relevant information when compared to other available diagnostic studies.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81504

81540

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

GENE EXPRESSION PROFILING TESTS FOR CANCERS OF UNKNOWN PRIMARY

Clinical Context Test Purpose

The purpose of tissue of origin testing is to identify a likely primary tumor type and by doing so inform treatment selection that might lead to improved health outcomes.

Recent advances in the understanding of gene expression in normal and malignant cells have led researchers to explore molecular classification to improve the identification of the site of origin of a cancer of unknown primary. The molecular classification of cancers is based on the premise that, despite different degrees of loss of differentiation, tumors retain sufficient gene expression “signatures” as to their cell of origin, even after metastasis. Theoretically, it is possible to build a gene expression database spanning many different tumor types to compare to the expression profile of very poorly differentiated tumors or a cancer of unknown primary to aid in the identification of the tumor type and organ of origin. The feasibility of using molecular classification schemes with gene expression profiling to classify these tumors of uncertain origin has been demonstrated in several studies.[4.5.6.7.](#)

Populations

The target populations are individuals with a cancer of unknown primary (CUP) and no identified primary tumor following a standard evaluation (e.g., history, physical, imaging, pathology).

Interventions

The Tissue of Origin test (formerly known as the PathWork Tissue of Origin Test and ResponseDX: Tissue of Origin; Cancer Genetics) measures the expression of 2000 genes and compares the similarity of the gene expression profiling of a cancer of unknown primary with a database of known profiles from 15 tissues with more than 60 histologic morphologies. The report generated for each tumor comprises a “similarity score,” which is a measure of similarity of gene expression profiling of the specimen to the profile of the 15 known tumors in the database. Scores range from 0 (very low similarity) to 100 (very high similarity), and sum to 100 across all 15 tissues on the panel. If a single similarity score is 30 or more, it indicates that this is likely the tissue of origin. If every similarity score is between 5 and 30, the test result is considered indeterminate, and a similarity score of less than 5 rules out that tissue type as the likely origin.

An alternative method to measure gene expression is real-time quantitative polymerase chain reaction. Real-time quantitative polymerase chain reaction can be used at the practice level; however, it can only measure, at most, a few hundred genes, limiting tumor categorization to 7 or fewer types. Tumor classification accuracy rates using real-time polymerase chain reaction have been reported to be as high as 87%, but lower (71%) the more undifferentiated the tumor tested.⁴ One assay that uses real-time quantitative polymerase chain reaction is the CancerTYPE ID (Biotheranostics) assay, which measures the expression of messenger RNA in a CUP tissue sample. Samples for this are formalin-fixed, paraffin-embedded tissue sections or unstained 10 mm sections on glass slides. Expression levels of 92 genes (87 tumor-associated genes and 5 reference genes for normalization) are used to detect 27 tumor types in a known database of 578 tumors with a range of 5 to 49 tumors per type. The report generated is the probability for the main cancer type, possible subtypes, tumor types not able to be excluded, and those ruled out with 95% confidence calculated by K nearest neighbor analysis. CancerTYPE ID is available with reflex to NeoTYPE Cancer Profile (NeoGenomics).

Comparators

The comparator of interest is standard of care management based on tumor type and probable site of origin—i.e., usual care without GEP.

Outcomes

Although test validity is relevant as a premise of the test, the outcomes informative of potential benefit include overall survival (OS), disease-specific survival, and quality of life.

Given the generally poor survival experience of patients with CUP, outcomes assessed over a follow-up of 1 to 2 years are relevant.

Study Selection Criteria

For the evaluation of clinical validity of these tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Specifically, for these tests, clinical validity is the ability of a test to determine the site of origin. Demonstrating clinical validity is complicated by the lack of reference standard. Imperfect reference standards must be relied on such as the available presumptive or a reference pathologic diagnosis, known tumor types, comparisons immunohistochemistry or primary tumor diagnosed during follow-up.

Tissue of Origin Test

Five included studies reported evidence that the Tissue of Origin Test can predict a likely site of origin using a variety of reference standards: reference or available diagnosis, a primary tumor identified during follow-up, and immunohistochemistry (IHC). Concordance rates in the range of 85% to 90% were reported compared with the reference standards employed.

The clinical validation study for the PathWork® Tissue of Origin test that was submitted to the FDA in 2008 involved a comparison of the gene expression profiles of 25 to 69 samples to each of the 15 known tumors on the PathWork® panel (average 36 specimens per known tumor).⁸ The specimens included poorly differentiated, undifferentiated and metastatic tumors. A similarity score was given to 545 specimens and then compared to the available specimen diagnosis. Based on the 545 results, the probability that a true tissue of origin call was obtained when a similarity score of 30 or more was reported was 92.9% (95% confidence interval [CI]: 90.3–95.0%), and the probability that a true-negative tissue call was made when a similarity score of 5 or less was reported was 99.7% (95% CI: 99.6–99.8%). Overall, the PathWork® performance comparing the profiles of the 545 specimens to the panel of 15 known tumor types showed a positive percent agreement of 90% (95% CI: 87%-92%), negative percent agreement of 100% (95% CI: 99–100%), non-agreement of 6 % (95% CI: 4 – 9%), and indeterminate of 4 % (95% CI: 3–7%).

The clinical validation study for the PathWork® Tissue of Origin test Kit-FFPE that was submitted to the U.S. Food and Drug Administration (FDA) in 2009 involved a comparison of the gene expression profiles of 25 to 57 samples to each of the 15 known tumors on the PathWork® panel (average 31 specimens per known tumor).⁹ The specimens included poorly differentiated, undifferentiated and metastatic tumors. A similarity score was given to 462 specimens and then compared to the available specimen diagnosis. Based on the 462 results, the probability that a true tissue of origin call was obtained when a similarity score was reported (positive percent agreement) was 89% (95% CI: 85 -91 %), and the probability that a true-negative (i.e., unknown) tissue call was made when a similarity score of 5 or less was reported was 99 % (95% CI: 98–100%). The proportion of nonagreement (false negatives) was 12% (95% CI, 9% to 15%). Further details of these data are available in FDA's decision summary.

In 2009, Monzon and colleagues conducted a multicenter-blinded validation study of the PathWork® test.¹⁰ The specimens included poorly differentiated, undifferentiated and metastatic tumors. A total of 351 frozen specimens and electronic files of microarray data on 271 specimens were obtained, with 547 meeting all inclusion criteria. A similarity score was given to the specimens, which was then compared to the original pathology report that accompanied the specimen. Overall, the PathWork® performance comparing the profiles of the 547 specimens to the panel of 15 known tumor types showed an overall agreement of 88% (95% CI: 85–90 %) with the reference diagnosis. Sensitivity and specificity were 88% (95% CI: 85–90 %) and 99 % (95% CI: 98 –100%), respectively, with the original pathology report acting as the reference standard. The authors acknowledged that since there was no independent confirmation of the original pathology, using the pathology reports as the reference standard could introduce errors into the study results. Agreement differed by site: 94 % for breast, 72% for both gastric and pancreatic. Performance differences between tissue sites were statistically different ($p=0.04$). Rates of agreement between test result and reference diagnosis varied by test center: 88%, 84.4%, 92.3%, and 89.7% for Clinical Genomics facility, Cogenics, Mayo Clinic, and the International Genomics Consortium, respectively, but these differences were not statistically significant.

In 2013, Azueta et al compared immunohistochemical (IHC) in FFPE tissue and the PathWork® test in archived fresh-frozen tissue in a series of 32 metastatic tumors of suspected gynecologic origin (25 metastatic to the ovary, 7 peritoneal metastases).¹¹ The primary site of origin was determined by clinical follow-up in 29 patients (83%) and was considered the gold standard. All peritoneal metastases originated from the ovary, and

metastases to the ovary originated from the colon (11 cases), breast (5 cases), stomach (4 cases), endometrium (1 case), and an angiosarcoma (1 case). Eligible frozen sections from these cases and 3 with cancer of unknown primary (CUP) were required to contain at least 60% tumor and less than 20% necrotic tissue. PathWork® concordance was 86% (25 of 29 diagnoses); in 2 cases, diagnoses were incorrect, and 2 cases had 2 possible diagnoses. PathWork® diagnosed 2 of 3 cases of unknown primary after clinical follow-up. IHC concordance was 79% (23 of 29 diagnoses); 4 cases were indeterminate, 2 cases had 2 possible diagnoses, and diagnoses of 2 of 3 cases of unknown primary after clinical follow-up matched the PathWork® diagnoses.

In 2013, Handorf et al reported a clinical validation study of 160 FFPE metastatic cancer specimens of known primary tumors representing the 15 tissue types on the PathWork® test panel.¹² PathWork® diagnostic performance was compared to IHC in 160 tumor samples. Overall concordance with known diagnoses (i.e., accuracy) was 89% for PathWork® and 83% for IHC, a statistically significant difference ($p=0.013$). In 51 poorly differentiated and undifferentiated tumors, PathWork® accuracy was 94%, and IHC accuracy was 79% ($p=0.016$). In 106 well-differentiated and moderately differentiated tumors, PathWork® and IHC performance was similar (87% and 85% accuracy, respectively; $p=0.52$). These results are based on 157 specimens for which both PathWork® and IHC were performed; three specimens from the original set of 160 were considered nonevaluable by PathWork® (similarity score <20) and were excluded.

CancerTYPE ID®

Results derived from 4 samples reported evidence for supporting the ability of CancerTYPE ID to predict a likely site of origin. Reference standards include a known tumor type, reference diagnosis, a primary tumor identified during follow-up, and IHC. Reported sensitivities varied according to tumor type generally ranged from 80% to over 90%.

Erlander et al (2011) revised the original classifier algorithm³ using 2206 samples created from multiple tumor banks and commercial sources.¹³ These samples expanded on the standard CancerTYPE ID® algorithm to increase tumor coverage and depth across 30 main cancer types and 54 histologic subtypes. Sensitivity of the classifier for the main cancer type based on internal validation (leave-one-out cross validation) was 87% (95% CL, 85% to 88%) and, for the histologic subtype, 85% (95% CL, 83% to 86%). In an independent test set of 187 samples, sensitivity was 83% (95% CI, 78% to 88%).

In 2012, Kerr et al reported on a multi-center study of the 92-gene CancerTYPE ID® was undertaken to assess the test's clinical validity.¹⁴ Approximately half of FFPE specimens for this study were from metastatic tumors of any grade, and the remainder from poorly differentiated primary tumors processed within 6 years of testing. Laboratory personnel at three study sites, blinded to all information except biopsy site and patient sex, performed diagnostic adjudication on 790 tumors, across 28-tumor types. Each specimen was then classified according to class or main type and subtype with the 92-gene assay. A similarity score of 85% or greater was specified a priori, as a threshold for classification with cases falling below this value determined to be unclassifiable by the test. When results of the 92-gene test were compared with adjudicated diagnoses, overall sensitivity of the 92-gene assay was 87% (95% CI, 84% to 89%) with a range of 48% to 100% within tumor types. The reference diagnosis was incorrectly ruled out in 5% of cases, and 6% remained unclassifiable. Test specificity was uniformly high in all tumor types, ranging from 98% to 100%. Positive predictive values ranged from 61% to 100% and exceeded 90% in 16 of 28 tumor types. In an

analysis of covariance, assay performance was found to be unaffected by tissue type (i.e., metastatic or primary), histologic grade, or specimen type. A 2014 substudy of this dataset evaluated primary (41%) and metastatic (59%) tumors considered having neuroendocrine differentiation (Merkel cell carcinoma, medullary thyroid carcinoma, pheochromocytoma, paraganglioma, pulmonary neuroendocrine carcinoma, pancreatic neuroendocrine carcinoma, and gastrointestinal neuroendocrine carcinoma).¹⁶ For 75 included tumors, assay sensitivities were 99% (95% CI, 0.93 to 0.99) for classification of neuroendocrine tumor type (e.g., neuroendocrine, germ cell) and 95% (95% CI, 0.87 to 0.98) for subtype (site of origin). Positive predictive values ranged from 83% to 100% for individual subtypes. A 2016 report by Brachtel et al examined a subset of samples from 109 patients with limited tissue studied by Kerr et al (2012) and 644 other consecutive cytology samples.¹⁷ In the 109 patients, sensitivity for tumor classification was 91% (95% CI, 84% to 95%) or consistent with the larger sample. From the 644 cases, a sensitivity of 87% (95% CI, 84% to 89%) was estimated.

In 2013, Greco et al published a retrospective, single-center study of 171 patients diagnosed with CUP after a clinical diagnostic work-up (i.e., before IHC).¹⁷ The purpose of the study was to evaluate the accuracy of gene expression profiling (CancerTYPE ID®) by verifying results with latent primary tumor sites found months after initial presentation (24 patients) or with IHC and/or clinicopathologic findings (147 patients). Minimum test performance thresholds were prespecified. Tumor specimens adequate for gene expression profiling were obtained in 149 patients (87%), and diagnoses were made in 144 (96%). Of 24 patients with latent primary tumor sites, CancerTYPE ID® diagnoses were accurate in 18 (75%), and IHC diagnoses were accurate in 6 (25%). Of 52 patients with diagnosis made by IHC and subsequent gene expression profiling, diagnoses matched in 40 (77%). When IHC suggested 2 or 3 possible primary sites (97 patients), CancerTYPE ID® diagnosis matched one of the proposed diagnoses in 43 (44%). Among 35 patients with discordant IHC and CancerTYPE ID® diagnoses, clinicopathologic correlates and subsequent IHC supported the CancerTYPE ID® diagnoses in 26 (74%). The authors concluded that gene expression profiling “complements standard pathologic evaluation” of CUP.

Consistent with other clinical validity data, Greco et al (2015) retrospectively reported on the use of CancerTYPE ID on archived samples from in 30 patients with CUP and poorly differentiated neoplasms.¹⁸ This subset of patients with CUP is considered potentially treatment sensitive, but comprised a small number (4%) of the 751 CUP patients evaluated from 2000 through 2012 at Tennessee centers. A primary site was identified in two patients. A diagnosis was assigned by GEP in 25 (83%) of the samples. Although 7 recently evaluated patients receive treatment based on the diagnosis provided, and 5 reportedly had “favorable” outcomes, whether benefit was obtained cannot be assessed.

Section Summary: Clinical Validity

To evaluate whether treatment selection can be improved, the ability of a test to suggest a likely site of origin (clinical validity) would typically be the first step in evaluation. Using different reference standards, these tests have reported sensitivities or concordances generally high (e.g., 80% to 90% or more). However, demonstrating clinical validity may be problematic because patients with cancers of unknown primary have no identified primary tumor for a reference standard. Imperfect reference standards must be relied on such as the available presumptive or a reference pathologic diagnosis, known tumor types, or comparisons immunohistochemical comparisons. A primary tumor diagnosed during follow-up might also be used as a reference standard, but its use would be subject to potential selection bias. Therefore, even substantial evidence supporting the ability of a test to suggest a likely site of

origin will be insufficient to infer benefit. Convincing evidence for benefit requires demonstrating that using a test to select treatment will improve outcomes.

Clinical Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. One published RCT and one conference presentation have been identified.

In 2019, Hayashi et al. randomized 130 patients with CUP to GEP-directed therapy based on the predicted tissue of origin or to empirically-directed chemotherapy with paclitaxel and carboplatin (see Table 1).²³ A total of 101 patients received the assigned treatment and were included in the analysis. There was no significant difference between the two groups in the 1-yr survival rate, OS, or PFS (see Table 2). For example, the 1-year survival rate was 44.0% for patients who received GEP-directed treatment and 54.9% for patients who received empirical chemotherapy ($P = .264$). The identification of more-responsive and less-responsive tissue types was prognostic for OS, (16.7 vs. 10.6 months; $p = .116$) and PFS (5.5 vs. 3.9 months; $p = .018$), both respectively. There were several limitations to this trial which included the high percentage of patients who did not receive the assigned treatment (see Tables 3 and 4). A major limitation in interpretation of these results is that during the trial period there were few treatments that were site specific, so there was minimal difference in the actual treatments given to the two groups.

The second is the Randomised Phase III Trial Comparing a Strategy Based on Molecular Analysis to the Empiric Strategy in Patients With Carcinoma of an Unknown Primary (CUP) (GEFCAPI 04) study that was presented at the 2019 Congress of the European Society for Medical Oncology in Barcelona.²⁴ The majority of patients in the experimental group were assessed with Cancer TYPE ID. For the entire group of experimental and control patients analyzed ($n=223$), there was no significant difference in OS (hazard ratio [HR]: 0.92, $p=0.71$) or PFS (HR: 0.95, $p<0.71$) between patients who received site-directed therapy or empirically directed therapy of cisplatin and gemcitabine. There were 60 patients who had a GEP test with a predicted site of origin that was likely to be insensitive to cisplatin and gemcitabine, among whom OS for the site-directed and control groups was also not significantly different (HR:0.74, $p=0.33$). However, the study was underpowered for this subgroup analysis. Median OS in the subgroup was not improved by GEP testing 9.1 mo [95% CI: 5.65;14.62] compared to the control group 10.87 mo [95% CI 3.45;11.73]. As in the study by Hayashi et al, using a molecular test followed by tailored systemic treatment did not improve outcomes in the total population of patients with CUP.

Table 2. Summary of Key RCT Characteristics

Study; Trial					Countries	
		Sites	Dates	Participants	Interventions	
					Active	Comparator
Hayashi et al (2019)	Japan	14	2008-2017	Patients with CUP (130 who were randomized and had sufficient tissue for analysis)	GEP-directed therapy (50 analyzed)	Empirically directed chemotherapy with PC (51 analyzed)
Fizazi et al (2019)	Europe	4	2012-2019	Patients with CUP (243)	GEP-directed therapy (110 mITT)	Empirically directed chemotherapy with CG (113 mITT)

CG: cisplatin and gemcitabine; CUP: cancer of unknown primary; mITT: modified intent to treat; PC: paclitaxel and carboplatin; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Results

Study	1-yr Survival Rate	Overall Survival (95% CI) mo	Progression Free Survival (95% CI) mo
Hayashi et al (2019)			
N	101	101	101
GEP-directed Therapy	44.0%	9.8 (5.7 to 13.8)	5.1 (1.9 to 8.3)
Empirical-PC	54.9%	12.5 (8.9 to 16.1)	4.8 (3.3 to 6.5)
HR (95% CI)		1.028 (0.678 to 1.560)	0.884 (0.590 to 1.326)
p-Value	0.264	0.896	0.550
Fizazi et al (2019)			
N		223	223
HR (95% CI)		0.92 (0.69-1.23)	0.95 (0.72-1.25)
p-Value		0.71	0.71

CI: confidence interval; GEP: gene expression profiling; HR: hazard ratio; RCT: randomized controlled trial.

Table 4. Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Hayashi et al (2019)		4. There were few treatments available at the time of the study that were site specific, resulting in little difference between the site specific and empiric chemotherapy treatments			

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Hayashi et al (2019)	4. Following randomization, if the assay were completed but the results could not predict a tissue of origin, patients were transferred to the empiric treatment arm.	1, 2, 3. No blinding		1. There was high loss to follow-up with 29 patients who did not receive the assigned therapy and were not included in the analysis	2. There was insufficient power due to the high loss to follow-up.	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Tissue of Origin Test

Nystrom et al (2012) enrolled 65 physicians (from 316 approached) caring for 107 patients with CUP in 2009 to participate in a study of management changes following a tissue of origin test.²⁵ Prior to the test, physicians had no suspected diagnosis for 54 (41%) patients, which declined to 17 (16%) after testing. Changes in management were reported in 70 (65%) patients. Physicians reported test results were helpful with regard to diagnosis, choosing therapy, and triaging. Median survival was 14 months, which the authors suggest longer than 9 months for unselected chemotherapy treated CUP patients. However, the low physician participation rate and lack of a concurrent comparator group limits any implications of these results. The study was supported by PathWork Diagnostics and 2 authors which are company employees.

Yoon et al (2016) reported results of a multicenter phase 2 trial evaluating combined use of carboplatin, paclitaxel, and everolimus in patients with CUP.²⁶ The primary outcome was objective response, and the study a 2-stage design with 11 or more responses in 50 assessable patients at the second stage considered success. There were 16 partial responses (objective response rate, 36%; 95% CI, 22% to 51%). Grade 3 or 4 adverse events occurred in 40 (87%) patients. Results from the PathWork Tissue of Origin Test were used post hoc to examine any association with response to therapy. In 38 of 46 patients, the test was successfully obtained and 10 different tissues of origin were predicted. In 19 patients with a tissue of origin where platinum/taxane therapy might be considered standard therapy, objective response rates were higher compared with other patients (53% vs. 26%, $p=0.097$), accompanied by longer progression-free survival (PFS; 6.4 months vs. 3.5 months, $p=0.026$; hazard ratio [HR], 0.47; 95% CI, 0.24 to 0.93), and longer OS (median, 17.8 months vs. 8.3 months; $p=0.005$; HR=0.37; 95% CI, 0.18 to 0.76). The results suggested a tissue of origin test might identify platinum/taxane-sensitive tumors. However, the study was not designed to evaluate predictive use of the test, tissue of origin data were missing for 17% of patients, and severe adverse events were common.

CancerTYPE ID

From patients with CUP who had undergone a CancerTYPE ID assay between March 2008 and August 2009, Hainsworth et al (2012) identified those with a probable ($\geq 80\%$) colorectal site of origin.²⁷ A total of 125 patients (of 1544 results) were predicted to have a primary colorectal cancer (CRC). Physicians caring for patients were sent questionnaires with a request for deidentified pathology reports—42 (34%) responded (physicians were paid \$250). The date of questionnaire mailing was not reported. A total of 32 patients were given CRC regimens (16 first-line therapy only, 8 first- and second-line therapy, 8 second-line therapy only) with a reported response rate of 50% following first-line and 50% following second-line therapy; 18 patients were given empiric CUP regimens with a response rate of 17%. For first-line therapies, physician-assessed PFS was longer following CRC regimens—8.5 months versus 6 months ($p=0.11$). The authors concluded that “Molecular tumor profiling seems to improve survival by allowing specific therapy in this patient subgroup....” However, conclusions are limited by significant potential biases: low physician response rates and potential selection bias; unverified physician-reported retrospective assessment of progression, response, or death; absence of information on patient performance status to assess between-group prognostic differences; and the post hoc subgroup definition of uncertain generalizability to patients with CUP undergoing tissue of origin testing.

In 2013, Hainsworth et al published a multi-site prospective case-series of the 92-gene CancerTYPE ID® assay.²⁸ FFPE biopsy specimens for this study included adenocarcinoma, poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or squamous carcinoma. A total of 289 patients were enrolled for this study, and 252 (87%) had adequate biopsy tissue for the assay. The molecular profiling assay predicted a tissue of origin in 247 (98%) of 252 patients. One-hundred nineteen assay predictions (48%) were made with $\geq 80\%$ similarity score and the rest were below 80% probability. Twenty-nine patients (12%) did not remain on study due to decreasing performance, brain metastases, or patient and physician decision. Of the remaining 223 patients, 194 (87%) received assay-directed chemotherapy, and 29 (13%) received standard empiric therapy. Median overall survival of the 194 patients receiving assay-directed chemotherapy was 12.5 months, which was found to exceed a prespecified improvement threshold of 30% compared with historical trial data on 396 performance-matched CUP patients receiving standard empiric therapy at the same center. Although these results are consistent with benefit from GEP testing in CUP, potential biases accompany the nonrandomized design—confounding variables, use of subsequent lines of empirical therapy, heterogeneity of unknown primary cancers—and limit conclusions that can be drawn.^{29,30}

Section Summary: Clinical Useful

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 CUP to receive treatment based on GEP results or usual care. One published RCT and one conference presentation with this design were identified. These trials did not find a survival benefit for patients with CUP 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 primary cancers were not insensitive 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 CUP may have clinical utility. The absence of convincing evidence from RCTs prevents conclusions about clinical utility.

SUMMARY OF EVIDENCE

For individuals who have a cancer of unknown primary (CUP) who receive gene expression profiling, the evidence includes studies of analytic validity, clinical validity, and limited evidence on potential clinical utility. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. For the 3 commercially available tests reviewed, there is some evidence to support relevant aspects of analytic validity; 1 test has been cleared by the Food and Drug Administration. 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, 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 CUP to receive treatment based on GEP results or usual care. One published RCT and one conference presentation with this design were identified. These trials did not find a survival benefit for patients with CUP 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 primary cancers were not insensitive 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 CUP may have clinical utility, but the absence of convincing evidence from RCTs prevents conclusions about clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

A currently unpublished trial that might influence this review is listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06140992	PaCIFIC-CUP classifies cancer of unknown primary origin	160	Dec 202
Unpublished			
NCT01540058	A Randomized Phase III Trial Comparing a Strategy Based on Molecular Analysis to the Empiric Strategy in Patients With Carcinoma of an Unknown Primary (CUP)	223	Aug 2019 (Conference Presentation)
NCT03278600	The Value of Tissue-of-origin Profiling in Predicting Primary Site and Directing Therapy in Patients With Cancer of Unknown Primary: a Prospective Randomized Controlled Study	172	Mar 2021 (status unknown)
NCT03498521	A Phase II, Randomized, Active-Controlled, Multi-Center Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Guided by Genomic Profiling Versus Platinum-Based Chemotherapy in Patients With Cancer of Unknown Primary Site Who Have Received Three Cycles of Platinum Doublet Chemotherapy (CUPISCO)	790	Jun 2024

NCT: national clinical trial

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines for the workup of an occult primary malignancy (v.2.2025) address the use of molecular methods to classify tumors.²⁶ The NCCN panel does not currently recommend use of gene sequencing to predict tissue of origin until more robust outcomes and comparative effectiveness data are available. NCCN guidelines state “consider tumor/somatic molecular profiling for patients who are candidates for anti-cancer therapy to identify uncommon mutations (i.e., RET fusions). Testing on tumor tissue is preferred; however cell-free DNA testing can be considered if tumor tissue testing is not feasible.

National Institute for Health and Clinical Excellence

A 2010 clinical guideline from the National Institute for Health and Clinical Excellence recommends against the use of gene expression profiling identifying primary tumors in patients with CUPs.²⁷ In the 2023 update, NICE withdrew recommendations on gene-expression-based profiling and added a link to the NHS Genomic Medicine Service’s national genomic test directory.

European Society of Medical Oncology (ESMO)³⁰

A 2022 guideline, Cancer of unknown primary: ESMO clinical practice guideline for diagnosis, treatment and follow-up, recommends the following:

- Histology and IHC on good quality tissue specimens are required [III, A].
- After lineage classification, a stepwise approach using further IHC markers, navigated by the clinical work-up results, is recommended [III, A].
- NGS may be carried out routinely in CUP [IV, B].
- The clinical utility of gene expression profiling to help elucidate the likely primary is not currently supported by high-level evidence. Consequently, it is not generally recommended outside of clinical research [II, D].

Government Regulations

National/Local:

There are no national Medicare coverage decisions for these tests, but local Medicare coverage decisions have been released for all 3 tests finding them to be “reasonable and necessary.”

A 2013 Technology Assessment was commissioned by Centers for Medicare and Medicaid for consideration by the MEDCAC panel.³² Studies identified evaluating CancerTYPE ID, miRview, and PathWorkDx through November 7, 2012, were included. The report concluded that all tests had similar accuracies, ranging from 85% to 88% (9 studies of PathWorkDx, 6 of CancerTYPE ID, 4 of MiRview), but that evidence was insufficient to evaluate the effect on management and outcomes. (Following review, the MEDCAC panel voted 2 [scale of 1 = low, 3 = intermediate, and 5 = high confidence] after considering the question: “How confident are you that there is sufficient evidence to determine whether genetic testing of tumor tissue affects health outcomes (including benefits and harms) for patients with cancer whose anticancer treatment strategy is guided by the results of each of the following?”)³³

In 2011, Palmetto GBA, the Medicare contractor in California, issued positive coverage for the PathWork® Tissue of Unknown Origin test. Because all tests are processed out of the

PathWork Diagnostics Laboratory in California, the test will be covered for Medicare patients in the United States. In 2012, Palmetto issued a similar statement for CancerTYPE ID®, and in 2013, Novitas issued a similar statement for MiRview® (Rosetta Cancer Origin™).

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing for Cytochrome P450 Polymorphisms

References

1. PDQ Adult Treatment Editorial Board. Carcinoma of Unknown Primary Treatment (PDQ). 2018; <https://www.ncbi.nlm.nih.gov/books/NBK65811/>. Accessed February 7, 2023.
2. Oien KA, Evans TR. Raising the profile of cancer of unknown primary. J Clin Oncol. Sep 20 2008; 26(27): 4373-5. PMID 18802148
3. Agwa E, Ma PC. Overview of various techniques/platforms with critical evaluation of each. Curr Treat Options Oncol. Dec 2013; 14(4): 623-33. PMID 24243164
4. 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): 465-73. PMID 16594740
5. 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): 15149-54. PMID 11742071
6. 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): 7388-93. PMID 11606367
7. 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): 4031-40. PMID 15899792
8. U.S. Food and Drug Administration. 510(k) Substantial Equivalence Determination Decision Summary: Pathwork Tissue of Origin Test. 2008; https://www.accessdata.fda.gov/cdrh_docs/reviews/K080896.pdf. Accessed November 2024.
9. U.S. Food and Drug Administration. 510(k) Substantial Equivalence Determination Decision Summary: Pathwork Tissue of Origin Test Kit-FFPE. 2010; https://www.accessdata.fda.gov/cdrh_docs/reviews/K092967.pdf. Accessed November 2024.
10. 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): 2503-8. PMID 19332734
11. 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): 20-8. PMID 22939961

12. 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): 1067-75. PMID 23648464
13. Erlander MG, Ma XJ, Kestly 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
14. 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): 3952-60. PMID 22648269
15. 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
16. Brachtel EF, Operaña 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): 27220-31. PMID 27034010
17. 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 05 2013; 105(11): 782-90. PMID 23641043
18. 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): 91-7. PMID 25758902
19. 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*. Mar 01 2019; 37(7): 570-579. PMID 30653423
20. 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.
21. 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): 620-8. PMID 22689213
22. 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): 339-44. PMID 26578722
23. 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): 112-8. PMID 22000811
24. 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): 217-23. PMID 23032625
25. 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
26. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: occult primary (cancer of unknown primary [CUP]). Version 2.2025. http://www.nccn.org/professionals/physician_gls/pdf/occult.pdf. Accessed November 2024.

27. National Institute for Health and Care Excellence (NICE). Metastatic malignant disease of unknown primary origin in adults: diagnosis and management [CG104]. 2010; <https://www.nice.org.uk/guidance/CG104>. Accessed November 2024.
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; <https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/downloads/id67a.pdf>. Accessed November 2023. No longer available.
30. Kramer A, Bochtler T, Pauli C, et al. Cancer of unknown primary: ESMO clinical practice guideline for diagnosis, treatment and follow-up. A. Oncology. December 2022; 34(3):228-246.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/10	1/4/10	12/8/09	Joint policy established
3/1/13	12/11/12	12/31/12	Routine update of non-covered service
11/1/13	8/22/13	8/27/13	Code update; added 81504 to policy. Policy otherwise unchanged.
11/1/14	8/21/14	8/25/14	Routine update, policy status unchanged.
3/1/16	12/10/15	12/10/15	Routine policy maintenance. References updated. New code added, 81540. Policy status unchanged.
3/1/17	12/13/16	12/13/16	Routine policy maintenance. Rationale and references updated. Medicare coverage updated. BCC reference deleted. Policy status unchanged.
3/1/18	12/12/17	12/12/17	Reorganized rationale section, added references 21, 29, 33, and 37-38. No change in policy status.
3/1/19	12/11/18		Routine policy update, no change in policy status.
3/1/20	12/17/19		Routine policy update, no change in policy status.
3/1/21	12/15/20		Routine policy update, references 23 and 24 added. No change in policy status.
3/1/22	12/14/21		Routine policy update, no change in policy status.
3/1/23	12/20/22		Routine policy update, no change in policy status.
3/1/24	12/19/23		MPS language clarified for policy intent. Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
3/1/25	12/17/24		Routine policy maintenance, no change in status. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING-MICROARRAY TESTING FOR CANCERS OF UNKNOWN
PRIMARY (CUP) ORIGIN

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A