

## Corporate Medical Policy

### Microarray-based Gene Expression Testing for Cancers of Unknown Primary

<b>File Name:</b>	microarray-based_gene_expression_testing_for_cancers_of_unknown_primary
<b>Origination:</b>	3/30/09
<b>Last CAP Review:</b>	8/2011
<b>Next CAP Review:</b>	8/2012
<b>Last Review:</b>	1/2012

#### Description of Procedure or Service

---

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. It is suggested that identifying a likely primary source and directing treatment accordingly may improve health outcomes.

##### **Cancers of Unknown Primary**

Cancers of unknown primary (CUP), or occult primary malignancies, are tumors that have metastasized from an unknown primary source; they make up approximately 3% of all cancer cases in the U.S. Identifying the primary origin of a tumor can dictate cancer-specific treatment, expected outcome and prognosis.

Most cancers of unknown primary 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 cancer of unknown primary include a thorough history and physical examination, CT scans of the chest, abdomen and pelvis, routine laboratory studies and targeted evaluation of specific signs and symptoms.

Biopsy of a cancer of unknown primary 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.

The current success rate of the diagnostic workup of a cancer of unknown primary is 20-30%, including consideration of clinical, radiologic, and extensive histopathologic methods. Recent advances in the understanding of gene expression in normal and malignant cells have led researchers to explore molecular classification as a way to improve the identification of the site of origin of a cancer of unknown primary.

##### **Molecular Classification of Cancers**

The molecular classification of cancers is based on the premise that, despite different degrees of

# Microarray-based Gene Expression Testing for Cancers of Unknown Primary

dedifferentiation, 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.

Ramaswamy and colleagues, using microarray gene expression analysis of more than 16,000 genes, showed 78% classification accuracy of 14 common tumor types. Su and colleagues, using large-scale RNA profiling with microarrays, accurately predicted the anatomical site of tumor origin for 90% of 175 carcinomas. Bloom et al. combined multiple tumor microarray databases, creating a large collection of tumors, including 21 types, resulting in a molecular classification scheme that reached 85% accuracy.

Although microarray technology enables large numbers of genes to be evaluated at the same time, it is complex and time-consuming and is limited in its use as mostly a research tool. In addition, since formalin fixation can degrade RNA, fresh/frozen tissue is preferred for better accuracy with microarray technology; however, formalin-fixed is the standard for pathology material in current practice.

One such microarray technology is the Pathwork® Pathchip. The test measures the expression of more than 1,500 genes and compares the similarity of the GEP of a CUP to a database of known profiles from 15 tissues with more than 60 histologic morphologies. The report generated for each tumor consists of a "similarity score," which is a measure of similarity of the GEP 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 greater than or equal to 30, 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 alternate method to measure gene expression is real-time quantitative polymerase chain reaction (RT-PCR). RT-PCR 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 RT-PCR have been reported to be as high as 87%, but less so (71%) the more undifferentiated the tumor tested.

## 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 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, 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 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 sub-classify or modify the classification of tumors that can be diagnosed by current clinical and pathologic practice, nor to predict disease course, or survival or

# Microarray-based Gene Expression Testing for Cancers of Unknown Primary

treatment efficacy, nor 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.

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## Policy

---

**Microarray-based gene expression profiling is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.**

## Benefits Application

---

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Microarray-based Gene Expression Testing for Cancers of Unknown Primary is covered

---

Not applicable.

## When Microarray-based Gene Expression Testing for Cancers of Unknown Primary is not covered

---

Gene expression profiling using the Pathwork® Tissue of Origin test or the Pathwork® Tissue of Origin test kit-FFPE to evaluate the site of origin of a tumor of unknown primary, and to distinguish a primary from a metastatic tumor is considered investigational for all indications.

## Policy Guidelines

---

The Pathwork® Tissue of Origin test has not been FDA-approved for use in cancer of unknown origin, nor has it been approved for differentiating metastatic from primary cancers. In addition, since the original policy was created in 2008, there have been no new data published on the clinical impact of the Pathwork® test. The impact of this testing on clinical outcomes (clinical utility) is

# Microarray-based Gene Expression Testing for Cancers of Unknown Primary

not currently known.

## Billing/Coding/Physician Documentation Information

---

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: There is no specific CPT or HCPCS code for this service.*

*Preparation of the probes may be coded using a combination of the molecular diagnostic codes 83890 - 83913. The analysis of the probes may be coded using array-based evaluation of multiple molecular probes codes 88384 - 88386 based on the number of probes analyzed. Pathwork Diagnostics states they use 84999 for claim submission.*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

---

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.54, 12/11/08

Senior Medical Director Review - 2/2009

Specialty Matched Consultant Advisory Panel - 8/2009

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.54, 11/11/2010

Specialty Matched Consultant Advisory Panel – 8/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.54, 11/10/2011

## Policy Implementation/Update Information

---

03/30/09 New policy adopted. Reviewed with Senior Medical Director 2/24/2009. Gene expression profiling using the Pathwork® Tissue of Origin test to evaluate the site of origin of a tumor of unknown primary, and to distinguish a primary from a metastatic tumor because it is considered investigational. Notice given 3/30/09. Effective date of policy 7/6/2009. (btw)

10/12/09 Specialty Matched Consultant Advisory Panel review 8/28/09. No changes to policy statement. (btw)

6/22/10 Policy Number(s) removed (amw)

9/30/11 Specialty Matched Consultant Advisory Panel review 8/31/11. “Description” section

# Microarray-based Gene Expression Testing for Cancers of Unknown Primary

updated. “Policy” statement revised, no change to intent. Added information to the “When Not Covered” section to include a new test for formalin-fixed paraffin-embedded (FFPE) specimens as investigational. References added. (btw)

2/7/12 Reference added. (btw)

---

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.