

## 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>	8/2018
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#### Description of Procedure or Service

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##### 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% to 4% of all cancers 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.

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 (GEP) to classify these tumors of uncertain origin has been demonstrated in several studies.

##### Tissue of Origin Testing, Treatment Selection, and Health Outcomes

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Patients with CUP have generally poor prognoses. For example, patients with disease limited to lymph nodes have a median survival of 6 to 9 months, and those with disease that is extranodal 2 to 4 months. 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 or as a predictive test. To evaluate whether treatment selection can be improved, the ability of test to suggest a likely site of origin (clinical validity) must be first be shown. But demonstrating clinical validity may be problematic because patients with CUPs 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 IHC. 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.

The Tissue of Origin test (formerly known as the PathWork Tissue of Origin Test and ResponseDX Tissue of Origin; Cancer Genetics). The test measures the expression of 2000 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 comprises a “similarity score,” which is a measure of similarity of 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 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. PathWork Diagnostics developed the test, but the company filed for bankruptcy in early 2013; Response Genetics purchased its assets, and it, in turn, was acquired by Cancer Genetics in late 2015.

An alternative method to measure gene expression is real-time quantitative polymerase chain reaction (RT-qPCR). RT-qPCR 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 (RT-PCR) have been reported to be as high as 87%, but lower (71%) the more undifferentiated the tumor tested.<sup>3</sup> One assay that uses RT-qPCR 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 (FFPE) tissue sections or unstained 10 micron 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.

miRview mets is another RT-qPCR test that uses microRNAs (miRNA), small noncoding, single-stranded RNA molecules that regulate genes posttranscription, as a signature for tumor differentiation. Expression levels of these miRNAs have been shown to be a sensitive biomarker across various pathologic conditions. Samples for this test are FFPE tissue. The miRview test used 48 panel markers to detect 22 tumor types in a known database of 336 tumors, with a range of 1 to 49 tumors per type. Results from the test provided a tumor of origin but may list multiple possibilities calculated by a binary decision tree and K nearest neighbor algorithm. A second-generation test, the RosettaGX Cancer Origin Test (formerly miRview mets2 and ProOnc Tumor Source), has also been developed; this test expands the number of tumor types to 49 primary origins with a panel of 64 miRNAs.

## Regulatory Status

In July 2008, test “PathWork® Tissue of Origin Test” (Response Genetics; now Cancer Genetics) 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

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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.

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.

The test is now offered by Cancer Genetics, as the Tissue of Origin® test.

Neither CancerType ID® nor miRview® (or Rosetta Cancer Origin™) have been submitted to the FDA for approval.

***\*\*\*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

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

## Benefits Application

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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

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Not applicable.

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

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Gene expression profiling is considered investigational to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor.

## Policy Guidelines

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Cancers of unknown primary (CUP) represent 3% to 4% of cancers diagnosed in the United States. These cancers are heterogeneous and many accompanied by poor prognoses. A detailed history and physical combined with imaging and tissue pathology can identify some, but not all, primary sources of

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secondary tumors. It is suggested that identifying the likely primary source with gene expression profiling to direct treatment accordingly may improve health outcomes.

For individuals who have a CUP who receive gene expression profiling, the evidence includes studies of clinical validity, and limited evidence on potential clinical utility. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. Of the 3 commercially available tests reviewed, one has been cleared by the 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 (eg, 80% to 90% or more). However, evidence for clinical validity does not support potential benefit. There is limited indirect evidence from nonrandomized studies on clinical utility, and all studies had significant limitations. Benefit would be most convincingly demonstrated through a marker strategy-designed trial randomizing patients with a CUP to treatment based on expression profiling results or to usual care. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Billing/Coding/Physician Documentation Information

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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.bcsnc.com](http://www.bcsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81479, 81504, 81540, G0452*

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

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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

Specialty Matched Consultant Advisory Panel – 8/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.54, 11/8/2012

Medical Director – 12/2012

Specialty Matched Consultant Advisory Panel – 8/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.54, 11/14/2013

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Specialty Matched Consultant Advisory Panel- 8/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.54, 11/13/2014

Specialty Matched Consultant Advisory Panel- 8/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.54, 11/12/2015

Specialty Matched Consultant Advisory Panel- 8/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.54, 3/9/2017

Specialty Matched Consultant Advisory Panel 8/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.54, 3/8/2018

Specialty Matched Consultant Advisory Panel 8/2018

## Policy Implementation/Update Information

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- 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 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)
- 9/4/12 Specialty Matched Consultant Advisory Panel review 8/15/2012. Description revised. No change to policy intent. (btw)
- 1/15/13 Removed the following statement from the Billing/Coding section; "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" Added codes 81479 and G0452 to Billing/Coding section. Description section updated. The When Not Covered section reworded from "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." to "Gene expression profiling is considered investigational to evaluate the site of origin of a tumor of unknown primary, or to

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- distinguish a primary from a metastatic tumor.” Policy Guidelines updated. Reference added. Medical Director review 12/18/2012. (btw)
- 9/10/13 Specialty Matched Consultant Advisory Panel review 8/21/2013. No change to policy. (btw)
- 12/31/13 Description section updated. Added CPT code 81504 to the Billing/Coding section. Reference added. (btw)
- 9/9/14 Specialty matched consultant advisory panel review 8/26/2014. No change to policy statement. (lpr)
- 1/13/15 Reference added. (lpr)
- 10/1/15 Specialty Matched Consultant Advisory Panel review 8/26/2015. No change to policy statement. (lpr)
- 12/30/15 Updated the Description and Policy Guidelines sections. Reference added. Added CPT code 81540 to Billing/Coding section for effective date 1/1/2016. (lpr)
- 9/30/16 Specialty Matched Consultant Advisory Panel review 8/31/2016. No change to policy statement. (lpr)
- 4/28/17 Updated Description and Policy Guidelines sections. Reference added. No change to policy statement. (lpr)
- 9/29/17 Specialty Matched Consultant Advisory Panel review 8/30/2017. No change to policy statement. (lpr)
- 4/13/18 Reference added. (lpr)
- 9/7/18 Specialty Matched Consultant Advisory Panel review 8/2018. No change to policy statement. (lpr)

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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.