



# Louisiana

## **Gene Expression-Based Assays for Cancers of Unknown Primary**

**Policy #** 00271

**Original Effective Date:** 10/20/2010

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### **Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of gene expression profiling (GEP) to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor to be **investigational**.\*

### **Policy Guidelines**

#### **Genetics Nomenclature Update**

The Human Genome Variation Society 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). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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.

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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

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

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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### **Background/Overview**

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

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

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; computed tomography scans of the chest, abdomen, and pelvis; routine laboratory studies; and targeted evaluation of specific signs and symptoms.

#### **Diagnosis and Classification**

Biopsy of a cancer of unknown primary with detailed pathology evaluation may include immunohistochemical analysis of the tumor. Immunohistochemical identifies different antigens present in different types of tumors and can usually distinguish an epithelial tumor (ie, 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 immunohistochemical 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

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gene expression profiling to classify these tumors of uncertain origin has been demonstrated in several studies.

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

About 80% of patients with cancer of unknown primary have a poor prognosis with a median survival of 3 to 10 months. 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 or as a predictive test. To evaluate whether treatment selection can be improved, the ability of a 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 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. 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.

### Tests Reviewed in This Report

Evidence on the clinical validity and clinical utility for 3 gene expression profiling tests is reviewed herein (see Table 1).

**Table 1. Gene Expression Profiling Tests for Cancers of Unknown Primary**

Test	Manufacturer	Platform	Test	Manufacturer
Tissue of Origin <sup>a</sup>	Cancer Genetics	Oligonucleotide microarray	Tissue of Origin <sup>a</sup>	Cancer Genetics
CancerTYPE ID	Biotheranostics	RT-qPCR	CancerTYPE ID	Biotheranostics
RosettaGX Cancer Origin <sup>b</sup>	Rosetta Genomics	RT-qPCR (microRNA)	RosettaGX Cancer Origin <sup>b</sup>	Rosetta Genomics

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Adapted from Agwa et al (2013).

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

<sup>a</sup> Formerly PathWork and ResponseDX: Tissue of Origin.

<sup>b</sup> Formerly miRview met<sup>2</sup>.

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. PathWork Diagnostics developed the test but 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. 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. 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 10µm 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 real-time quantitative polymerase chain reaction test that uses microRNAs (miRNA), small noncoding, single-stranded RNA molecules that regulate genes posttranscription,

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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 formalin-fixed, paraffin-embedded 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 mets<sup>2</sup> 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.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

In 2008, the PathWork<sup>®‡</sup> Tissue of Origin Test<sup>™‡</sup> (Response Genetics; now Cancer Genetics) 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.

The test is now offered by Cancer Genetics, as the Tissue of Origin<sup>®‡</sup> test.

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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<sup>®‡</sup> (Biotheranostics, San Diego, CA) and miRview<sup>®‡</sup> (or RosettaGX Cancer Origin<sup>™‡</sup>; Rosetta Genomics, Philadelphia, PA) are 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.

### **Rationale/Source**

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

For individuals who have cancers of unknown primary who receive gene expression profiling, the evidence includes studies of clinical validity, and 2 randomized control trials (RCTs) that have evaluated 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 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 (eg, 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 cancers of unknown primary to receive treatment based on gene expression profiling 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 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 primary cancers were not insensitive to the control treatments.

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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 the effects of the technology on health outcomes.

The objective of this evidence review is to evaluate whether gene expression profiling in patients with cancers of unknown primary improves the net health outcome compared with standard of care management based on tumor type and probable site of origin.

## **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.2.2020) address the use of molecular methods to classify tumors. The guidelines state: “Tumor sequencing and gene signature profiling for tissue of origin is not recommended for standard management at this time.” A footnote acknowledges that “there may be diagnostic benefit, though not necessarily clinical benefit. The use of gene signature profiling is a category 3 recommendation [based on any level of evidence, there is major NCCN disagreement that the intervention is appropriate].” The guidelines later note:

“In an attempt to identify the tissue of origin, biopsy specimens are often analyzed by immunohistochemistry (IHC). Gene expression profiling (GEP) assays have also been developed to attempt to identify the tissue of origin in patients with occult primary cancers... Thus far the literature on GEP has focused far more on establishing a tissue of origin than on determining whether such identification leads to better outcomes in patients. Thus, while there may be diagnostic benefit of GEP, a clinical benefit has not been demonstrated.”

#### **National Institute for Health and Care Excellence**

A 2010 clinical guidance from the National Institute for Health and Care Excellence recommended against the use of gene expression profiling to identify primary tumors in patients with cancers of unknown primary. This recommendation was based on “limited evidence that gene-expression based profiling changes the management of patients with cancer of unknown primary and no evidence of

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improvement in outcome.” The guidance included a research recommendation for trials to assess the clinical utility of gene expression profiling.

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

A 2013 technology assessment was commissioned by Centers for Medicare & Medicaid for consideration by the MEDCAC panel. Studies identified evaluating CancerTYPE ID, miRview, and PathWorkDx through November 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?”)

There are no national Medicare coverage decisions for these tests, but local Medicare coverage decisions for all 3 tests have found them to be “reasonable and necessary.” In 2011, Palmetto GBA, issued positive coverage for the PathWork Tissue of Unknown Origin Test. Because all tests are processed out of the company 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.

### Ongoing and Unpublished Clinical Trials

A currently unpublished trial that might influence this review is listed in Table 2.

**Table 2. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT03278600	The Value of Tissue-of-origin Profiling in Predicting Primary Site and Directing Therapy in	172	Sep 2020

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	Patients With Cancer of Unknown Primary: a Prospective Randomized Controlled Study		
<i>Unpublished</i>			
NCT01540058	A Randomised 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)

NCT: national clinical trial.

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10/20/2010 Medical Policy Implementation Committee approval.  
06/14/2012 Medical Policy Committee review  
06/20/2012 Medical Policy Implementation Committee approval. A new test for formalin-fixed paraffin-embedded (FFPE) specimens added to the investigational statement.  
01/23/2013 Coding updated  
05/02/2013 Medical Policy Committee review  
05/22/2013 Medical Policy Implementation Committee approval. Coverage statement changed to be generalizable to gene expression profiling and not specific to the Pathwork test.  
05/01/2014 Medical Policy Committee review  
05/21/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
05/07/2015 Medical Policy Committee review  
05/20/2015 Medical Policy Implementation Committee approval. Title change. Coverage eligibility unchanged.  
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.  
01/01/2016 Coding update  
02/03/2016 Coding update  
05/05/2016 Medical Policy Committee review  
05/18/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes  
05/04/2017 Medical Policy Committee review

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# Louisiana

## Gene Expression-Based Assays for Cancers of Unknown Primary

Policy # 00271

Original Effective Date: 10/20/2010

Current Effective Date: 06/08/2020

05/17/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/01/2018 Coding update

05/03/2018 Medical Policy Committee review

05/16/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

08/07/2018 Coding update

10/29/2018 Coding update

01/01/2019 Coding update

05/02/2019 Medical Policy Committee review

05/15/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

05/07/2020 Medical Policy Committee review

05/13/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2021

### **Coding**

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

*The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy*

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*Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81406, 81479, 81504, 81540
HCPCS	No codes
ICD-10 Diagnosis	C00.0-C26.9, C30.0-C34.92, C37-C38.8, C40.0-C41.9, C43.20-C58, C60.0-C69.52, C43.11-C43.122, C71.9-C86.6, C88.2-C91.42, C96.0-C96.Z, D03.0-D03.9, D04.111-D04.122, D22.111-D22.122, D23.111-D23.122

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

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### 3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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