Medical Policy
Gene Expression‒Based Assays for Cancers of Unknown Primary

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 614
BCBSA Reference Number: 2.04.54
NCD/LCD:
- Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35025)
- Local Coverage Article: MolDX: bioTheranostics Cancer TYPE ID® Update (A53101)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

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.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the links below.

Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35025)

Local Coverage Article: MolDX: bioTheranostics Cancer TYPE ID® Update (A53101)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient
For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Product Description</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO Blue™</td>
<td>Prior authorization is not required.</td>
</tr>
<tr>
<td>Medicare PPO Blue™</td>
<td>Prior authorization is not required.</td>
</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81540</td>
<td>Oncology (tumor of unknown origin), MRNA, gene expression profiling by real-time rt- pcr of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype</td>
</tr>
</tbody>
</table>

**Description**

CANCERS OF UNKNOWN PRIMARY
Cancers of unknown primary (CUPs), or occult primary malignancies, are tumors that have metastasized from an unknown primary source; they make up approximately 3% to 4% of all cancers in the United States. Identifying the primary origin of a tumor can dictate cancer-specific treatment, expected outcome, and prognosis.

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

Diagnosis and Classification
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 (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 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 CUP. 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 CUP 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**

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.

**Tests Reviewed in This Report**

Evidence on the analytic validity, clinical validity, and clinical utility for 3 GEP tests is reviewed in this report (see Table 1).

**Table 1. Gene Expression Profiling Tests for CUP**

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Platform</th>
<th>Genes Assayed, n</th>
<th>Tumor Types Assessed, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue of Origin®a</td>
<td>Cancer Genetics</td>
<td>Oligonucleotide microarray</td>
<td>2000</td>
<td>15</td>
</tr>
<tr>
<td>CancerTYPE ID®</td>
<td>Biotheranostics</td>
<td>RT-qPCR</td>
<td>92</td>
<td>54</td>
</tr>
<tr>
<td>RosettaGX Cancer Origin™, b</td>
<td>Rosetta Genomics</td>
<td>RT-qPCR (microRNA)</td>
<td>64</td>
<td>49</td>
</tr>
<tr>
<td><strong>CUP:</strong> cancer of unknown primary; RT-qPCR: real-time quantitative polymerase chain reaction.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Formerly PathWork® and ResponseDX: Tissue of Origin™.
b Formerly miRview® met.

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.³ 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.

Summary
For individuals who have a 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 (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.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/2017</td>
<td>BCBSA National medical policy review. Policy clarified. 5/1/2017</td>
</tr>
<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541) added.</td>
</tr>
<tr>
<td>2/2014</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
</tbody>
</table>

Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
References


29. Prasad V, Oseran A, Fakhrejahani 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;64:159-162. PMID 26608119