**Description**

Cancers of unknown primary (CUP) represent 3% of all cancer cases in the United States. 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 with microarray-based gene expression testing and directing treatment accordingly may improve health outcomes.

**Related Policies**

- N/A

**Policy**

Gene expression profiling is considered **investigational** for either of the following:

- To evaluate the site of origin of a tumor of unknown primary
- To distinguish a primary from a metastatic tumor

**Policy Guidelines**

Effective January 1, 2014, there is a specific CPT code for the Pathwork Tissue of Origin test:

- **81504**: Oncology (tissue of origin), microarray gene expression profiling of >2000 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as tissue similarity scores

Prior to 2014, Pathwork Diagnostics stated that they used 84999 (unlisted chemistry procedure).

The other tests described (see Rationale section) do not have specific CPT codes. If the test result is calculated using an algorithm and reported as a numeric score(s) or as a probability, the following CPT code would be reported:

- **81599**: Unlisted multianalyte assay with algorithmic analysis

If it is not calculated using an algorithm, then the following CPT code would be reported:

- **81479**: Unlisted molecular pathology procedure
**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Rationale**

**Background**

**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% of all cancer cases in the U.S. Identifying the primary origin of a tumor can dictate cancer-specific treatment, expected outcome, and prognosis.(1)

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)

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. Results of IHC may provide a narrow differential of possible sources of a tumor’s origin, but not necessarily a definitive answer.

Current success rate of the diagnostic workup of a CUP is 20% to 30%, including consideration of clinical, radiologic, and extensive histopathologic methods.(3) 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 CUP.

**Molecular Classification of Cancers**

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 with the expression profile of very poorly differentiated tumors or a CUP to aid in the identification
of the tumor type and organ of origin. Feasibility of using molecular classification schemes with gene expression profiling (GEP) to classify these tumors of uncertain origin has been demonstrated in several studies.(4-7)

Ramaswamy et al (2001), using microarray gene expression analysis of more than 16,000 genes, showed 78% classification accuracy of 14 common tumor types.(5) Su et al (2001), using large-scale RNA profiling with microarrays, accurately predicted the anatomical site of tumor origin for 90% of 175 carcinomas.(6) Bloom et al (2004) combined multiple tumor microarray databases, creating a large collection of tumors, including 21 types, resulting in a molecular classification scheme that reached 85% accuracy.(8) Although microarray technology enables large numbers of genes to be evaluated simultaneously, it is complex and time-consuming and is limited to use primarily as a research tool.(4) Additionally, 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.(9)

One such microarray technology is the ResponseDX: Tissue of Origin™ test (formerly known as the Pathwork® Tissue of Origin Test; Response Genetics Inc., Los Angeles, CA). The test measures the expression of more than 1500 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. The test was developed by Pathwork Diagnostics, but the company filed for bankruptcy in early 2013, and their assets were purchased by Response Genetics Inc.

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.(4) One assay that uses RT-qPCR is the CancerType ID® (bioTheranostics Inc., San Diego, CA) 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 (Rosetta Genomics, Philadelphia, PA) 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 utilizes 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 provide 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 Rosetta Cancer Origin Test™ (formerly MiRview® mets2), has
recently been developed; this test expands the number of tumor types to 42 primary origins with a panel of 64 miRNAs.

**Regulatory Status**

In July 2008, the Pathwork® Tissue of Origin test 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 histopathological 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, and prostate cancers; thyroid carcinoma; 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 subclassify or modify the classification of tumors that can be diagnosed by current clinical and pathologic practice, nor to predict disease course, or survival or 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 was cleared for marketing by FDA through the 510(k) process. The 2010 clearance is an expanded application, which allows the test to be run on a patient’s 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 substantially equivalent to the previously approved device by FDA through the 510(k) process.

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

**Literature Review**

Assessment of a diagnostic technology typically focuses on 3 analyses:

1. Analytic validity including comparison with a reference standard test and test/retest reliability. However, because of the lack of a reference standard for determining definitive diagnoses of cancers of unknown primary (CUP) origin, assessment of analytic validity for these tests relies on test/retest reliability.
2. Clinical validity including sensitivity, specificity, and positive and negative predictive value in appropriate populations of patients.
3. Clinical utility (i.e., demonstration that information from the diagnostic test leads to improved health outcomes).
Three gene expression-based profiling tests currently available in the U.S. are the primary focus of this review (Table 1).

Table 1. Characteristics of Gene Expression-Based Assays for CUP Currently Available in the U.S.(10)

<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>ResponseDX: Tissue of Origin® (a)</td>
<td>Response Genetics</td>
<td>Oligonucleotide microarray</td>
<td>&gt;1500</td>
<td>15</td>
</tr>
<tr>
<td>CancerType ID®</td>
<td>bioTheranostics</td>
<td>RT-qPCR</td>
<td>92</td>
<td>54</td>
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<tr>
<td>Rosetta Cancer Origin® (b)</td>
<td>Rosetta Genomics</td>
<td>RT-qPCR (microRNA)</td>
<td>48</td>
<td>42</td>
</tr>
</tbody>
</table>

CUP: cancer of unknown primary; n: number; RT-qPCR: real-time quantitative polymerase chain reaction; (a) Formerly Pathwork®; (b) Formerly miRview® met2

ResponseDX: Tissue of Origin Test™ (Formerly Pathwork®)

Analytic Validity

Fresh Frozen Tumor Sample

In 2008, Dumur et al analyzed performance characteristics of the Pathwork® Tissue of Origin test in a cross-laboratory comparison study of 60 poorly and undifferentiated metastatic (77%) and primary (23%) tumors.(11) Three academic and 1 commercial laboratory received archived frozen tissue specimens for procurement and processing at their individual sites. Steps performed by each of the 4 laboratories included tissue handling, RNA extraction, and microarray-based gene expression assays using standard microarray protocol. The resulting microarray data generated at each laboratory were sent in a blinded fashion to Pathwork Diagnostics for generation of similarity scores for each type. Reports of the similarity scores were sent back (blinded) to the pathologists at the 4 laboratories for their use in generating an interpretation. Data were compared among the 4 laboratories to determine assay reproducibility. Correlation coefficients were between 0.95 and 0.97 for pathologists’ interpretations of the similarity scores, and cross-laboratory comparisons showed an average 93.8% overall concordance between laboratories in terms of final tissue diagnosis.

Formalin-Fixed, Paraffin-Embedded Tumor Sample

Analytical performance characteristics of the Pathwork® test for formalin-fixed, paraffin-embedded (FFPE) were analyzed in a cross-laboratory comparison study of 60 poorly and undifferentiated metastatic (45%) and primary (35%) tumors. Each of the 15 tumor tissue types were represented by 4 specimens each, with the exception of breast (n=3) and soft tissue sarcoma (n=5). Samples were distributed among 3 laboratories for procurement and processing at their individual sites. Data were compared among the 3 laboratories to determine assay reproducibility. Correlation coefficients were between 0.92 and 0.93 for pathologists’ interpretations of the similarity scores, and cross-laboratory comparisons showed an average 82.1% overall concordance between laboratories in terms of final tissue diagnosis. A detailed summary of the data is available in the Food and Drug Administration’s (FDA) decision summary.(12) Additional analyses of the analytic performance of the test have produced similar results.(13,14)
Clinical Validity

Fresh Frozen Tumor Sample

The clinical validation study for the Pathwork® Tissue of Origin test that was submitted to the FDA in 2008 involved a comparison of gene expression profiles of 25-69 samples with each of the 15 known tumors on the Pathwork® panel (mean: 36 specimens per known tumor). Specimens included poorly differentiated, undifferentiated, and metastatic tumors. A similarity score was assigned to 545 specimens and then compared with 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 93% (95% confidence interval [CI], 90% to 95%), and the probability that a true-negative tissue call was made when a similarity score of 5 or less was reported was 100% (95% CI, 100% to 100%). Overall Pathwork® performance comparing the profiles of the 545 specimens with the panel of 15 known tumor types showed a positive percent agreement of 90% (95% CI, 87% to 92%), negative percent agreement of 100% (95% CI, 99% to 100%), nonagreement of 6% (95% CI, 4% to 9%), and indeterminate of 4% (95% CI, 3% to 7%).

In 2009, Monzon et al conducted a multicenter blinded validation study of the Pathwork® test.(15) 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 with the original pathology report that accompanied the specimen. The Pathwork® performance comparing the profiles of the 547 specimens to the panel of 15 known tumor types showed overall sensitivity (positive percent agreement with reference diagnosis) of 88% (95% CI, 85% to 90%) and overall specificity (negative percent agreement with reference diagnosis) of 99% (95% CI, 98% to 100%), 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 error into study results. Agreement differed by cancer type: 94% for breast and 72% for both gastric and pancreatic; these differences were statistically significant ($\chi^2=42.02; p=0.04; df=28; n=547$). Rates of agreement between test result and reference diagnosis varied by testing center: 88%, 84%, 92%, and 90% for Clinical Genomics facility, Cogenics, Mayo Clinic, and the International Genomics Consortium, respectively, but these differences were not statistically significant.

In 2012, 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).(16) 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% (25/29 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% (23/29 diagnoses); 4 cases were indeterminate, and two cases had two possible diagnoses; diagnoses of 2 of 3 cases of unknown primary after clinical follow-up matched the Pathwork® diagnoses.
FFPE Tumor Sample

The clinical validation study for the Pathwork® Tissue of Origin test Kit-FFPE that was submitted to the FDA in 2009 involved a comparison of the gene expression profiles of 25-57 samples to each of the 15 known tumors on the Pathwork® panel (mean: 31 specimens per known tumor). Specimens included poorly differentiated, undifferentiated, and metastatic tumors. A similarity score was assigned to 462 specimens and then compared with 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% to 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 (negative percent agreement) was 99% (95% CI, 98% to 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.(12)

In 2013, Handorf et al reported a clinical validation study of FFPE metastatic cancer specimens of known primary tumors representing the 15 tissue types on the Pathwork® test panel.(17) Pathwork® diagnostic performance was compared with 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; 3 specimens from the original set of 160 were considered nonevaluable by Pathwork® (similarity score <20) and were excluded.

Clinical Utility

One ongoing and one completed randomized trial are designed to test clinical utility and clinical application of gene expression profiling (GEP) to patient management and tumor site-specific therapy of the Pathwork® Tissue of Origin test. See the “Ongoing and Unpublished Clinical Trials” below for further information.

CancerType ID®

Analytic Validity

FFPE Tumor Sample

Erlander et al (2011) assessed the analytic performance characteristics of the 92-gene CancerType ID® test.(18) A training set of 2557 tumor samples was created from multiple tumor banks and commercial sources with 2206 samples included in the final internal validation dataset. These samples expanded on the standard CancerType ID® algorithm to increase tumor coverage and depth across 30 main cancer types and 54 histologic subtypes. Reproducibility was calculated from the observed cycle time for the 92 genes and 5 normalization genes using positive and negative controls. A total of 194 independent runs that included 4 operators provided the overall mean percentage coefficient of variation (CV) for the positive controls, which were 1.69% and 2.19% for the 92-genes and 5 normalization genes, respectively; for the negative controls the CV was 1.25% and 1.66% for the 92 genes and 5 normalization genes, respectively.

Clinical Validity

FFPE Tumor Sample

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).(19) 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.

In 2012, Kerr et al reported on a multicenter study of the 92-gene CancerType ID® test conducted to assess the test’s clinical validity.(20) Approximately half of FFPE specimens for this study were from metastatic tumors of any grade, and the remainder were from poorly differentiated primary tumors processed within 6 years of testing. Laboratory personnel at 3 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. Similarity score of 85% or greater was specified 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%-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%-100%. Positive predictive values exceeded 90% in 16 of 28 tumor types (57%), with an overall range of 61%-100%. In ANCOVA subgroup analysis, 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 to have neuroendocrine differentiation (Merkel cell carcinoma, medullary thyroid carcinoma, pheochromocytoma, paraganglioma, pulmonary neuroendocrine carcinoma, pancreatic neuroendocrine carcinoma, and gastrointestinal neuroendocrine carcinoma).(21) 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 0.83 to 1.00 for individual subtypes.

In 2011, Erlander et al investigated clinical performance characteristics of the 92-gene CancerType ID® test.(18) A training set of 2557 tumor samples was created from multiple tumor banks and commercial sources. After excluding samples for inadequate tumor content, inconsistent or inconclusive pathologic information based on independent review, or cycle threshold (cycle number at which the generated fluorescence exceeds the fluorescence threshold) greater than 28, a total of 2206 samples were included in the final internal validation dataset. Samples all underwent real-time polymerase chain reaction (RT-qPCR) with the 92-gene assay primer-probe to serve as inputs for a modification to the standard CancerType ID® classification algorithm. Overall sensitivity of the CancerType ID® test determined by cross-validation was 87% (95% CI, 85% to 88%) for main tumor type with specificity of 100% (95% CI, 99% to 100%). Positive predictive value for main type accuracy was 87% and negative predictive value was 100%. For tumor subtypes these values were similar with a sensitivity of 85% (95% CI, 83% to 86%), specificity
of 100% (95% CI, 100% to 100%), positive predictive value of 85%, and negative predictive value of 100%. One hundred eighty-seven independently collected tissue samples with specimens derived from formalin-fixed, paraffin-embedded blocks (84%) and snap-frozen tissues (16%) also were used to test the performance of the new algorithm. This test set included 28 of the 30 main cancer types and had an overall sensitivity of 83% and ranged from 50% to 100% across individual tumor types.

Clinical Utility
In 2013, Hainsworth et al published a multisite prospective case-series of the 92-gene CancerType ID® assay. (22) FFPE biopsy specimens for this study included adenocarcinoma, poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or squamous carcinoma. A total of 289 patients were enrolled, 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 a similarity score of 80% or greater, and the rest were below 80% probability. Twenty-nine patients (12%) did not remain on study due to decreasing performance status, 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 who received assay-directed chemotherapy (67% of the original patient sample) 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 who received standard empiric therapy at the same center. Due to potential biases introduced by the nonrandomized design, confounding variables, such as use of subsequent lines of empirical therapy, and heterogeneity of unknown primary cancers, conclusions that can be drawn from this study are limited. (23)

Rosetta Cancer Origin™ (formerly miRview® mets2)

Analytic Validity
FFPE Tumor Sample
A 2011 study by Chajut et al provided information on the analytic validity of the miRview® mets2 test. (24) One hundred seventy-four FFPE specimens were independently tested by Rosetta Genomics research and development laboratory and by a CLIA-approved clinical laboratory to determine concordance of the microRNA (miRNA) profiles. Interlaboratory concordance was greater than 95% in 160 (92%) of 174 samples.

Clinical Validity
FFPE Tumor Sample
In 2012, Meiri et al assessed the clinical validity of the miRview® mets2 test in 509 FFPE specimens. (25) Four hundred eighty-nine of these samples were successfully processed, and results were compared with the known origin of the specimen. Sensitivity of the test was 86%, and specificity exceeded 99%. Three smaller clinical validation studies testing 83-204 samples reported similar sensitivity and specificity, with ranges of 84%-86% and 95%-99%, respectively. (26-28)

Clinical Utility
No published data on the clinical utility of miRview® mets2 and impact on patient treatment decision or diagnosis has been identified in the literature.
Other Microassay Tests for CUP

Clinical Validity

FFPE Tumor Sample

Other studies have analyzed the clinical validity of microarray gene expression technology. One 2008 study used microarray technology (CupPrint®, Agendia; Amsterdam, the Netherlands) in FFPE tumor samples. CupPrint® uses the same internal validation data set as CancerType ID® and is currently marketed outside of the U.S. The study analyzed 495 genes in 84 patients with tumors of known origin and 38 patients with CUP to assess potential contribution to patient management. Sixteen (48%) patients with CUP had their primary site of tumor origin identified by standard laboratory techniques. Molecular testing identified the correct site of tumor origin in 94% of cases of CUP and 83% of tumors of known origin.

Ades et al (2013) compared gene expression profiling (CupPrint®) to standard clinical work-up in patients with newly diagnosed, untreated metastatic tumors. The authors prespecified a minimum concordance threshold of 75% to establish the diagnostic accuracy of CupPrint®. Of 67 prospectively enrolled patients, both CupPrint® and clinical diagnoses were obtained in 31 (46%). Median time to diagnosis was significantly shorter with CupPrint® than with clinical workup (10 days vs 48 days, respectively; p < 0.001). Diagnoses were concordant in 11 patients (35%). The authors concluded that the diagnostic accuracy of CupPrint® is low.

Clinical Utility

A small 2008 study of CupPrint® retrospectively analyzed the GEP of FFPE tumor samples from 21 patients with CUP. In all patients, standard methods had failed to determine a primary tumor origin. GEP results were reviewed in the context of tumor histology and clinical suspicion of tumor origin; the clinical relevance of results and implications for patient management were assessed. Gene expression profiling confirmed clinical suspicion in 16 of 21 patients (76%). There was clinical/GEP inconsistency in 4 of 21 patients (19%) and histologic/gene profile inconsistency in 1 patient (5%). The authors concluded that the use of GEP would have influenced patient management in 12 (57%) of 21 patients.

Ferracin et al (2011) published a report of microRNA profiling in 101 FFPE tumor samples from primary cancers and metastases. Forty samples of 10 cancer types were used to build a cancer-type-specific microRNA signature. This signature was then used to predict the primary site of metastatic cancer. Overall accuracy was 100% for primary cancers and 78% for metastatic cancers in the cohort sample. The signature was then applied to a published set of 170 samples; prediction rates were consistent with cohort results.

Ongoing and Unpublished Clinical Trials

A search of online site, ClinicalTrials.gov, returned 2 clinical trials to directly test the clinical utility and clinical application of GEP to patient management and tumor site-specific therapy.

- A randomized European phase 3 trial (NCT01540058) began in March 2012 with a completion date of October 2016. A treatment strategy guided by Pathwork® Tissue of Unknown Origin analysis followed by treatment for the suspected primary cancer is compared with an empiric strategy in patients with CUP. The study's primary outcome is progression from date of randomization, and secondary outcomes include tumor response rate, toxicity, and overall survival.
A clinical trial of miRview® mets was completed in April 2012 (NCT01202786) in Israel. The trial investigated the cost-effectiveness of using the miRview® test compared with conventional workup of patients with cancer of unknown primary origin. Sixty participants were enrolled, and the following data were collected: cost and time of the diagnostic process from day 1 of the study to the decision on treatment program, the concordance between the miRview® result compared with standard workup, treatment response, and overall survival. This trial has not been published.

Summary of Evidence
Available literature suggests that microarray-based gene expression testing may yield a high prediction rate in identifying CUP when comparing results to a known tissue of origin. However, without data on how these tests would alter clinical practice and clinical health outcomes (clinical utility), the investigational policy statement remains unchanged. A trial that randomizes patients with a cancer of unknown primary to receive treatment based on results of these types of tests or based on standard diagnostic procedures would be useful to determine clinical utility of gene-expression testing of CUPs.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
Current National Comprehensive Cancer Network (NCCN) guidelines for the workup of an occult primary malignancy (version 1.2015) address the use of molecular methods in the classification of tumors.(32) The guidelines state, “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 upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate].”

National Institute for Health and Clinical Excellence
A 2010 clinical guideline from the National Institute for Health and Clinical Excellence (NICE) recommended against the use of GEP to identify primary tumors in patients with cancers of unknown primary origin (CUP).(33) This recommendation is based on “limited evidence that gene-expression based profiling changes the management of patients with CUP and no evidence of improvement in outcome.” The guideline included a research recommendation for trials to assess the clinical utility of gene expression profiling.

European Society of Medical Oncology
A 2011 guideline from the European Society of Medical Oncology (ESMO) asserted that the impact of commercially available GEP assays for identifying tissue of origin in patients with CUP “via administration of primary site-specific therapy remains questionable and unproven in prospective trials (Level of recommendation: IV based on level D evidence [evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies; there is little or no systematic or empirical evidence]).(34) Rather, “Immunohistochemistry should be applied meticulously in order to identify the tissue of origin and to exclude chemosensitive and potentially curable tumors (i.e., lymphomas and germ cell tumors).”
Medical Policy

U.S. Preventive Services Task Force Recommendations

Molecular diagnostic testing for cancers of unknown primary origin is not a preventive service.

Medicare National Coverage

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.”

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 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®.

References


**Documentation Required for Clinical Review**

- History and physical and/or consultation notes including:
  - Reason for gene expression test
- Radiological reports (e.g., CT, MRI, PET)
- Labs including biopsy results (if applicable)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services are considered investigational and therefore not covered for any indication.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT®</td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>CPT®</td>
<td>81504</td>
<td>Oncology (tissue of origin), microarray gene expression profiling of &gt;2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported</td>
</tr>
</tbody>
</table>
Medical Policy

as tissue similarity scores
81599 Unlisted multianalyte assay with algorithmic analysis

HCPC | None
---|---
ICD-9 Procedure | None

ICD-10 Procedure | For dates of service on or after 10/01/2015
---|---
ICD-9 Diagnosis | All Diagnoses

ICD-10 Diagnosis | For dates of service on or after 10/01/2015
---|---
All Diagnoses

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/28/2013</td>
<td>New Policy Adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>3/7/2014</td>
<td>Coding and Administrative Update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>12/31/2014</td>
<td>Policy title change from Microarray-Based Gene Expression Testing for Cancers of Unknown Primary Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.
Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.