IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Gene expression tests have been developed to help identify the tissue of origin of tumors of unknown primary. These tests are proposed to assist in guiding treatment decisions.

MEDICAL POLICY CRITERIA

Gene expression profiling is considered investigational to evaluate the site of origin of a tumor of unknown primary, and to distinguish a primary from a metastatic tumor. Gene expression tests for this indication include, but are not limited to, the ResponseDX®:Tissue of Origin Test, the ResponseDX®:Tissue of Origin test kit-FFPE, CancerTypeID®, miRview®, and Rosetta Cancer Origin Test™.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
BACKGROUND

Cancers of unknown primary (CUPs), or occult primary malignancies, represent 3% to 4% of cancers diagnosed in the United States. These cancers are heterogeneous and many accompanied by poor prognoses. The current success rate of the diagnostic workup of a cancer of unknown primary is 20%–30%, including consideration of clinical, radiologic, and extensive histopathologic methods.[1] Recent advances in the understanding of gene expression in normal and malignant cells have led researchers to explore molecular classification as a way to improve the identification of the site of origin of a cancer of unknown primary. The benefit of identifying cancers of unknown primary is to identify appropriate cancer-specific treatment, expected outcome and prognosis.

The molecular classification of cancers is based on the premise that, despite different degrees of loss of differentiation, tumors retain sufficient gene expression “signatures” related 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.

One such microarray technology is the ResponseDX®: Tissue of Origin Test (Response Genetics, Inc., Los Angeles, CA), formerly known as the Pathwork® Tissue of Origin Test. The test measures the expression of more than 1,500 genes and compares the similarity of the gene expression profile of a cancer of unknown primary to a database of known profiles from 15 tissues with more than 60 histologic morphologies. The report generated for each tumor consists of a "similarity score," which is a measure of similarity of the gene expression profile of the specimen to the profile of the 15 known tumors in the database. Scores range from 0 (very low similarity) to 100 (very high similarity), and sum to 100 across all 15 tissues on the panel. If a single similarity score is greater than or equal to 30, it indicates that this is likely the tissue of origin. If every similarity score is between five and 30, the test result is considered indeterminate, and a similarity score of less than five rules out that tissue type as the likely origin. The test was developed by Pathwork Diagnostics, but was later purchased by Response Genetics, Inc.

MiRview® mets (Rosetta Genomics, Philadelphia, PA) is another microarray technology which uses microRNAs (miRNA), small non-coding, single-stranded RNA molecules that regulate genes post-transcription, as a signature for tumor differentiation. The 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 (FFPE) tissue. The MiRview test utilizes 48 panel markers used to detect 22 tumor types in a known database of 336 tumors with a range of 1 to 49 tumors per type. The results from the test provide a tumor of origin but may list multiple possibilities. A second generation test, the Rosetta Cancer Origin Test™ (formerly miRview® mets²), has recently been developed, which expands the number of tumor types to 42 primary origins with a panel of 64 miRNAs.
An alternative method to measure gene expression is real-time quantitative polymerase chain reaction (RT-PCR). RT-PCR can be used at the practice level; however, it can only measure, at most, a few hundred genes, limiting tumor categorization to seven or fewer types. Tumor classification accuracy rates using RT-PCR have been reported to be as high as 87%, but less so (71%) the more undifferentiated the tumor tested.\[2\] One assay that uses qRT-PCR is the CancerTypeID® (CancerTypeID; bioTheranostics, Inc., San Diego, CA) assay, which measures the expression of messenger RNA in a cancer of unknown primary (CUP) tissue sample. Samples for this are FFPE tissue sections or unstained 10 micron sections on glass slides. The expression levels of 92 genes (87-tumor associated genes and five 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.

**REGULATORY STATUS**

In July 2008, the ResponseDX®: Tissue of Origin Test (Response Genetics, Inc., Los Angeles, CA), formerly known as the Pathwork® Tissue of Origin Test, was cleared with limitations* for marketing by the 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 pathological practice. The database contains examples of RNA expression patterns for fifteen common malignant tumor types including bladder, breast, colorectal, gastric, hepatocellular, kidney, non-small cell lung, ovarian, pancreatic, prostate, and thyroid carcinomas, melanoma, testicular germ cell tumor, non-Hodgkins lymphoma (not otherwise specified), and soft tissue sarcoma (not otherwise specified). The ResponseDX®: 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:^[3]\]

The ResponseDX®: Tissue of Origin Test is not intended to establish the origin of tumors that cannot be diagnosed according to current clinical and pathological 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 pathological practice, nor to predict disease course, or survival or treatment efficacy, nor to distinguish primary from metastatic tumor. Tumor types not in the ResponseDX®: Tissue of Origin Test database may have RNA expression patterns that are similar to RNA expression patterns in tumor types in the database, leading to indeterminate results or misclassifications.

In June 2010, the “Pathwork® Tissue of Origin Test Kit-FFPE” (Pathwork Diagnostics) was cleared for marketing by the FDA through the 510(k) process. The 2010 clearance is an expanded application which allows the test to be run on a patient's FFPE tumor, and has the same indications and limitations. As of late 2013, the Tissue of Origin Test is distributed by Response Genetics, Inc.
To date, the CancerTypeID®, miRview® or Rosetta Cancer Origin Test™ tests have not been submitted to the FDA for approval.

EVIDENCE SUMMARY

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

The analytical and clinical validity of gene expression profiling to evaluate cancers of unknown primary (CUPs) has already been established. Therefore, the evidence review below will focus on the clinical utility of these tests.

The Agency for Healthcare Research and Quality (AHRQ) published a technology assessment in 2013 to review commercially available genetic tests used to identify the tissue of origin (TOO) of the cancer in patients with cancer of unknown primary (CUP).[4] AHRQ reviewed three genomic TOO tests (CancerTypeID, miRview, and PathworkDx) for analytical validity, clinical validity, and clinical utility. The review found very little evidence that supported the clinical usefulness of any of the three tests in making diagnosis and treatment decisions. The review also found very little evidence that the use of any of the three tests increased the length of survival among CUP patients who received the test. AHRQ determined that the evidence was insufficient to assess the ability of the tests to impact treatment or outcomes. Several of the key studies assessed in the AHRQ review, as well as studies published after the review, are described below.

ResponseDX®: TISSUE OF ORIGIN TEST AND ROSETTA CANCER ORIGIN™

There has been one study published that reports evidence of the clinical utility of the ResponseDX test. Nystrom et al. enrolled 65 physicians (from 316 approached) caring for 107 patients with CUP in 2009 to participate in a study of management changes following a tissue of origin test.[5] Prior to the test, physicians had no suspected diagnosis for 54 patients (41%), which declined to 17 (16%) after testing. Changes in management were reported in 70 patients (65%). Physicians reported test results were helpful with regard to diagnosis, choosing therapy, and triaging. However, the absence of a comparator physician and patient sample limits any implications of these results.

CancerTypeID®

In 2013, Hainsworth and colleagues conducted a multi-site prospective case-series of the 92-gene CancerTypeID assay.[6] The molecular profiling assay predicted a tissue of origin in 247 (98%) of 252 patients. One-hundred nineteen assay predictions were made with ≥80% similarity score and the rest were below 80% probability. Twenty-nine patients did not remain on study due to decreasing performance, brain metastases, or patient and physician decision. Of the remaining 223 patients, 194 (87%) received assay-directed chemotherapy, and 29 received standard empiric therapy. The median overall survival of the 194 patients receiving
assay-directed chemotherapy was 12.5 months, which was found to be within the a priori-specified improvement target of 30% compared with historical trial data on 396 performance-matched CUP patients receiving 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 are limited.

**PRACTICE GUIDELINE SUMMARY**

**NATIONAL COMPREHENSIVE CANCER NETWORK NCCN**

The NCCN guidelines for the workup of an occult primary malignancy address the use of molecular methods in the classification of tumors. The guideline states that “Tumor sequencing and gene signature profiling for tissue of origin is not recommended for standard management at this time.” The use of the gene signature profiling is a category three recommendation, which is based on any level of evidence and there is disagreement that the intervention is appropriate. NCCN states that although these assays may have diagnostic benefit, clinical benefit has not been demonstrated.[7]

**SUMMARY**

There is not enough research to show that tumor gene expression testing can improve survival or other health outcomes for people with cancer of unknown primary. Also, there are no clinical guidelines based on research which recommend the use of these tests to classify cancers of unknown primary. Therefore, gene expression profiling is considered investigational to identify cancers of unknown primary.

**REFERENCES**

6. Hainsworth, JD, Rubin, MS, Spigel, DR, et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of


### CODES

**NOTE:** Coding note would be entered here to explain something related to the codes listed in the policy.

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*Date of Origin: January 2011*