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*The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is not required but is recommended if, despite this Protocol position, you feel this service is medically necessary; supporting documentation must be submitted to Utilization Management.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Description

Cancers of unknown primary (CUP) represent 3% of all cancer cases in the U.S. 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.

Background

Cancers of Unknown Primary

Cancers of unknown primary (CUP), or occult primary malignancies, are tumors that have metastasized from an unknown primary source; they make up approximately 3% 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 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 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. The results of IHC may provide a narrow differential of possible sources of a tumor's origin, but not necessarily a definitive answer.

The current success rate of the diagnostic workup of a CUP is 20–30%, 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 cancer of unknown primary.

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

Ramaswamy and colleagues, using microarray gene expression analysis of more than 16,000 genes, showed 78% classification accuracy of 14 common tumor types. (5) Su and colleagues, using large-scale RNA profiling with microarrays, accurately predicted the anatomical site of tumor origin for 90% of 175 carcinomas. (6) Bloom et al 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 at the same time, it is complex and time-consuming and is limited in its use as mostly a research tool. (4) In addition, 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 Pathwork® (Response Genetics, Inc., Los Angeles, CA). The test measures the expression of more than 1,500 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 consists of a “similarity score,” which is a measure of similarity of the GEP of the specimen to the profile of the 15 known tumors in the database. Scores range from zero (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 the company filed for bankruptcy in early 2013, and their assets were 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 one to 49 tumors per type. The 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, 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. (4) 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 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 five 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, test “Pathwork® Tissue of Origin” (Pathwork Diagnostics, Inc., Sunnyvale, CA) 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 pathologic 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, prostate, and thyroid carcinomas, melanoma, testicular germ cell tumor, non-Hodgkin’s 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 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 formalin-fixed, paraffin-embedded (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 the U.S. Food and Drug Administration (FDA) through the 510(k) process.

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

Policy (Formerly Corporate Medical Guideline)

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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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