Gene Expression‒Based Assays for Cancers of Unknown Primary

Description
Cancers of unknown primary (CUPs) 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.

FDA REGULATORY STATUS
In July 2008, the PathWork® Tissue of Origin Test™ (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 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. The database contains examples of RNA expression patterns for 15 common malignant tumor types.

A PathWork® Tissue of Origin® Test result was 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 (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.

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 was an expanded application, which permitted 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 FDA through the 510(k) process. The test is now offered by Cancer Genetics, as the Tissue of Origin® test.
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.

**POLICY GUIDELINES**

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**RATIONALE**

**Summary of Evidence**

For individuals who have a cancer of unknown primary (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.

**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.2.2017) 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). In addition, gene expression profiling (GEP) assays have been developed to attempt to identify the tissue of origin in patients with occult primary cancers. It is noteworthy that thus far the literature on this approach, as with the literature on IHC application in the workup of occult primary tumors, has focused far more on establishing a tissue of origin than on establishing whether such identification leads to better outcomes in patients. Thus, while there is diagnostic benefit of GEP, a clinical benefit has not been demonstrated. Consequently, the panel does not recommend tumor sequencing and gene signature profiling for the identification of tissue of origin as standard management in the diagnostic workup of patients with occult primary tumors. Overall, the panel believes that neither IHC, a diagnostic tool in widespread use, nor GEP should be used indiscriminately.”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

A 2013 Technology Assessment was commission by Centers for Medicare and Medicaid for consideration by the MEDCAC panel. Studies identified evaluating CancerTYPE ID, miRview, and PathWorkDx through November 7, 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 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


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
FEP 2.04.54 Gene Expression–Based Assays for Cancers of Unknown Primary


POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>September 2012</td>
<td>New</td>
<td>Policy updated with literature search; references 14-21 added. Other tests commercially available besides Pathwork were added to the policy. Policy statement changed to be generalizable to gene expression profiling and not specific to Pathwork test.</td>
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<tr>
<td>March 2013</td>
<td>Revise Policy</td>
<td>Policy updated with literature review; references 14, 15, 17, 25, and 29 updated. No change to policy statement.</td>
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<tr>
<td>March 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 10, 12, 21, 23, and 34 added; reference 1, 24, 32-33, updated. Title changed to reflect range of gene expression test types. No change to policy statement.</td>
</tr>
<tr>
<td>March 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review through January 25, 2017 and selected citations from publications submitted by Biotheranostics; references added; some references deleted. Rationale reorganized and revised to reflect new literature and change of ResponseDX Tissue of Origin Test to Tissue of Origin. Policy statement changed to investigational.</td>
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