Gene Expression-Based Assays for Cancers of Unknown Primary

Policy # 00271
Original Effective Date: 10/20/2010
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Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of gene expression profiling (GEP) to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor to be **investigational.***

Background/Overview

Cancers of Unknown Primary

Cancers of unknown primary, or occult primary malignancies, are tumors that have metastasized from an unknown primary source; they make up about 3% of all cancers in the United States.

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 cancer of unknown primary 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

Cancers of unknown primary can be classified into 4 categories. Adenocarcinomas compose approximately 70% of cancers of unknown primary. Neuroendocrine tumors compose

approximately 1%, squamous cell carcinomas 5% and poorly differentiated cancer 20% to 25% of cancers of unknown primary.

Biopsy of a cancer of unknown primary with detailed pathology evaluation may include immunohistochemical analysis of the tumor. Immunohistochemical identifies different antigens present in 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 immunohistochemical analysis may provide a narrow differential of possible sources of a tumor's origin, but not necessarily a definitive answer.

Treatment Selection and Health Outcomes

Treatment is based on the histologic type and clinical features. About 20% of patients with cancer of unknown primary have features that guide treatment. However, about 80% of patients with cancer of unknown primary have a poor prognosis with a survival of 3–6 months despite a variety of chemotherapeutic combinations. Multiple sites of involvement are observed in about 50% of patients, commonly in the lungs, liver, bones and lymph nodes. The premise of tissue of origin testing in cancers of unknown primary is that identifying a likely primary tumor site will inform treatment selection leading to improved survival and other outcomes.

Tests Reviewed in This Report

Selected gene expression profiling tests are described in Table 1.

Table 1. Gene Expression Profiling Tests for Cancers of Unknown Primary

Test	Manufacturer	Platform	Genes Assayed, n	Tumor Types Assessed, n
Tissue of Origin[a]	Cancer Genetics	Oligonucleotide microarray	2000	15
CancerTYPE ID	Biotheranostics	RT-qPCR	92	54
RosettaGX Cancer Origin[b]	Rosetta Genomics	RT-qPCR (microRNA)		4

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Adapted from Agwa et al (2013).
RT-qPCR: real-time quantitative polymerase chain reaction.
[a] FormerlyPathWork and ResponseDX: Tissue of Origin.
[b] Formerly miRview met[2] This test does not appear to be currently available.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 2008, the PathWork®‡ Tissue of Origin Test™‡ (Response Genetics; now Cancer Genetics, Cancer Genetics merged with StemoniX in 2020.) was cleared for marketing with limitations (see below) by the U.S. Food and Drug Administration (FDA) through the 510(k) process (FDA product code: OIW), with subsequent clearances for expanded applications in 2010 and minor modifications in 2012. 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.

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.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). CancerTYPE ID®‡ (Biotheranostics, San Diego, CA) is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

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Rationale/Source

Description

Cancers of unknown primary 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.

Summary of Evidence

For individuals who have cancers of unknown primary who receive gene expression profiling, the evidence includes studies of clinical validity, and 2 randomized controlled trials (RCTs) that have evaluated clinical utility. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. Of the 2 commercially available tests reviewed, one has been cleared by the U.S. Food and Drug Administration (Tissue of Origin). For these tests, the clinical validity is the ability of a test to determine the site of origin. 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, the reference standard is imperfect, and evidence for clinical validity does not support potential benefit. Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with and without the test. The benefit would be most convincingly demonstrated through a trial randomizing patients with cancers of unknown primary to receive treatment based on gene expression profiling results or usual care. One published RCT and one conference presentation with this design were identified. These trials did not find a survival benefit for patients with cancers of unknown primary who received treatment based on the site of origin as determined by molecular testing. A limitation in interpretation of the published trial results is that there were few treatments that were site specific, so there was minimal difference in the actual treatments given to the two groups. In the second RCT, most cancers responded to the control treatments. Therefore, the possibility remains that if more site-specific treatments are developed, molecular testing to determine the site of origin in patients with cancers of unknown primary may have clinical utility, but the absence of convincing evidence from RCTs prevents conclusions about clinical utility. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network (NCCN) guidelines for the workup of an occult primary malignancy (v.2.2021) address the use of molecular methods to classify tumors. The use of gene expression 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). Gene expression profiling (GEP) assays have also been developed to attempt to identify the tissue of origin in patients with occult primary cancers… Thus far the literature on GEP has focused far more on establishing a tissue of origin than on determining whether such identification leads to better outcomes in patients. While there may be diagnostic benefit of GEP, a clinical benefit has not been demonstrated."

National Institute for Health and Care Excellence
A 2010 clinical guidance from the National Institute for Health and Care Excellence recommended against the use of gene expression profiling to identify primary tumors in patients with cancers of unknown primary. This recommendation was based on "limited evidence that gene-expression based profiling changes the management of patients with cancer of unknown primary and no evidence of improvement in outcome." The guidance included a research recommendation for trials to assess the clinical utility of gene expression profiling.

U.S. Preventive Services Task Force Recommendations
Not applicable.

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Policy # 00271
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Medicare National Coverage
A 2013 technology assessment was commission by Centers for Medicare & Medicaid for consideration by the MEDCAC panel. Studies identified evaluating CancerTYPE ID, miRview, and PathWorkDx through November 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?")

Medicare MolDX carriers (Noridian, Novitas, Palmetto, Wisconsin Physician Services, and CGS Administrators) decisions for PathWork Tissue of Unknown Origin Test and Cancer TYPE ID have found them to be "reasonable and necessary.".

Ongoing and Unpublished Clinical Trials
A currently unpublished trial that might influence this review is listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03498521	A Phase II, Randomized, Active-Controlled, Multi-Center Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Guided by Genomic Profiling Versus Platinum-Based Chemotherapy in Patients With Cancer of Unknown Primary Site Who Have Received Three Cycles of Platinum Doublet Chemotherapy (CUPISCO)	790	Jun 2023
Unpublished			

NCT01540058	A Randomised Phase III Trial Comparing a Strategy Based on Molecular Analysis to the Empiric Strategy in Patients With Carcinoma of an Unknown Primary (CUP)	243	Aug 2019 (Conference Presentation)
NCT03278600	The Value of Tissue-of-origin Profiling in Predicting Primary Site and Directing Therapy in Patients With Cancer of Unknown Primary: a Prospective Randomized Controlled Study	172	Sep 2020 (status unknown)

NCT: national clinical trial.

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10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. A new test for formalin-fixed paraffin-embedded (FFPE) specimens added to the investigational statement.
01/23/2013	Coding updated
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Coverage statement changed to be generalizable to gene expression profiling and not specific to the Pathwork test.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. Title change. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016	Coding update
02/03/2016	Coding update
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2018	Coding update
05/03/2018	Medical Policy Committee review

Coding

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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81406, 81479, 81504, 81540
HCPCS	No codes
ICD-10 Diagnosis	C00.0-C26.9, C30.0-C34.92, C37-C38.8, C40.0-C41.9, C43.20-C58, C60.0-C69.52, C43.11-C43.122, C71.9-C86.6, C88.2-C91.42, C96.0-C96.Z, D03.0-D03.9, D04.111-D04.122, D22.111-D22.122, D23.111-D23.122

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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