Protocol

Gene Expression-Based Assays for Cancers of Unknown Primary

(20454)

Medical Benefit		**Effective Date**: 04/01/18	**Next Review Date**: 01/19
Preauthorization	No	**Review Dates**: 05/09, 03/10, 01/11, 01/12, 01/13, 01/14, 01/15, 01/16, 01/17, 01/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. 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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With cancer of unknown primary	Interventions of interest are: • Gene expression profiling	Comparators of interest are: • Standard clinical management based on tumor type and probable site of origin	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life

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.

Summary of Evidence

For individuals who have a 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 three commercially available tests reviewed, there is some evidence to support relevant aspects of analytic validity; one test has been cleared by the Food and Drug Administration (FDA). 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 (e.g., 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.

Policy

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

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

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

Medicare Advantage

For Medicare Advantage the following tests will be considered **medically necessary**:

Cancer TYPE ID (Biotheranostics).

Tissue of Origin (Cancer Genetics Incorporated).

Molecular testing, using the ROSETTA Cancer Origin Test™ (PROG), is considered **medically necessary** in the pathologic diagnoses of CUP when a conventional surgical pathology/imaging work-up is unable to identify a primary neoplastic site. Other applications of this technology are considered **investigational** in the use of diagnosis of specific tumor types such as NSCLC and renal cancers.

Background

Cancers of Unknown Primary

CUPs, or occult primary malignancies, are tumors that have metastasized from an unknown primary source; they make up approximately 3% to 4% of all cancers in the United States. 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 CUPs. The most common primary sites of CUPs 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 scans of the chest, abdomen, and pelvis; routine laboratory studies; and targeted evaluation of specific signs and symptoms.[2]

Diagnosis and Classification

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 melanoma or sarcoma. Detailed cytokeratin panels often allow further classification of 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.

Recent advances in the understanding of gene expression in normal and malignant cells have led researchers to explore molecular classification to improve the identification of the site of origin of a CUP. 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 CUP 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.[3-6]

Tissue of Origin Testing, Treatment Selection, and Health Outcomes

Patients with CUP have generally poor prognoses. For example, patients with disease limited to lymph nodes have a median survival of six to nine months, and those with disease that is extranodal two to four months.[7] The premise of tissue of origin testing in CUPs is that identifying a likely primary tumor site will inform treatment selection leading to improved survival and other outcomes or as a predictive test. To evaluate whether treatment selection can be improved, the ability of test to suggest a likely site of origin (clinical validity) must be first be shown. But demonstrating clinical validity may be problematic because patients with CUPs have no identified primary tumor for a reference standard. Imperfect reference standards must be relied on such as the available presumptive or a reference pathologic diagnosis, known tumor types, or comparisons IHC. A primary tumor diagnosed during follow-up might also be used as a reference standard, but its use would be subject to potential selection bias. Therefore, even substantial evidence supporting the ability of a test to suggest a likely site of

origin will be insufficient to infer benefit. Convincing evidence for benefit requires demonstrating that using a test to select treatment will improve outcomes.

Tests Reviewed in This Report

Evidence on the analytic validity, clinical validity, and clinical utility for three GEP tests is reviewed in this report (see Table 1).

Table 1. Gene Expression Profiling Tests for CUP[8]

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)	64	49

CUP: cancer of unknown primary; RT-qPCR: real-time quantitative polymerase chain reaction.
[a] Formerly PathWork® and ResponseDX: Tissue of Origin™.
[b] Formerly miRview® met[2].

The Tissue of Origin test (formerly known as the PathWork Tissue of Origin Test and ResponseDX Tissue of Origin; Cancer Genetics). The test measures the expression of 2000 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 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 30 or more, 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. PathWork Diagnostics developed the test, but the company filed for bankruptcy in early 2013; Response Genetics purchased its assets, and it, in turn, was acquired by Cancer Genetics in late 2015.

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 seven 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.[3] One assay that uses RT-qPCR is the CancerTYPE ID (Biotheranostics) 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 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.

miRview mets 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 used 48 panel markers to detect 22 tumor types in a known database of 336 tumors, with a range of one to 49 tumors per type. Results from the test provided 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 RosettaGX Cancer Origin Test (formerly miRview mets[2] and ProOnc Tumor Source), has also been developed; this test expands the number of tumor types to 49 primary origins with a panel of 64 miRNAs.

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 (e.g., 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.

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

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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