Protocol

Gene Expression-Based Assays for Cancers of Unknown Primary

(20454)

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

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: • Usual care	Relevant outcomes include: • Test validity • Overall survival • Disease-specific survival

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 probable primary source with gene expression profiling and directing treatment accordingly may improve health outcomes.

Summary of Evidence

The evidence for gene expression profiling in patients who have CUP includes primarily studies of analytic validity and clinical validity, together with limited indirect evidence concerning potential clinical utility. Relevant outcomes are test validity as well as overall and disease-specific survival. Available evidence supports the analytic validity of these tests and that gene expression testing can often identify the site of origin for a CUP compared with a known tissue origin. Most studies were observational designs, often lacking a prospective component. A prospective single-arm trial suggested possible benefit over historical controls. One identified study found physicians reporting management changes following receipt of test results. Benefit would be most convincingly demonstrating through a marker strategy–designed trial randomizing patients with a cancer of unknown primary to receive treatment based on expression profiling results or usual care. Accordingly, 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.

Medicare Advantage

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

Cancer TYPE ID developed by bioTheranostics, effective date of 07/25/11.

Tissue of Origin developed by Pathworks effective date of 07/25/11.

Background

Cancers of Unknown Primary

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 cancers of unknown primary. 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 (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. Results of IHC may provide a narrow differential of possible sources of a tumor's origin, but not necessarily a definitive answer.

Current success rate of the diagnostic workup of a CUP is 20% to 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 CUP.

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 CUP to aid in the identification of the tumor type and organ of origin. 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 et al (2001), using microarray gene expression analysis of more than 16,000 genes, showed 78% classification accuracy of 14 common tumor types.[5] Su et al (2001), using large-scale RNA profiling with microarrays, accurately predicted the anatomic site of tumor origin for 90% of 175 carcinomas.[6] Bloom et al (2004) 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]

One such microarray technology is the ResponseDX: Tissue of Origin™ test (formerly known as the PathWork® Tissue of Origin Test; Response Genetics Inc., Los Angeles, CA). The test measures the expression of more than 1500 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 their assets.

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.[4] One assay that uses RT-qPCR is the CancerTYPE ID® (bioTheranostics Inc., San Diego, CA) 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 (Rosetta Genomics, Philadelphia, PA) 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 utilized 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 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® mets[2] and ProOnc Tumor Source), has recently been developed; this test expands the number of tumor types to 42 primary origins with a panel of 64 miRNAs.

Regulatory Status

In July 2008, the PathWork® Tissue of Origin Test™ was cleared for marketing with limitations* 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: bladder, breast, colorectal, gastric, hepatocellular, kidney, non-small-cell lung, ovarian, pancreatic, and prostate cancers; thyroid carcinomas; melanoma; testicular germ cell tumor; non-Hodgkin 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., CUP)

- 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 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. 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.

Neither CancerTYPE ID® nor miRview® (or Rosetta Cancer Origin™) has been submitted to FDA for approval.

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.

1. National Cancer Institute (NCI). U.S. National Institutes of Health. Carcinoma of unknown primary: treatment, 02/23/2012. Physician data query (PDQ®). http://www.cancer.gov/cancertopics/pdq/treatment/unknownprimary/healthprofessional. Accessed October 20, 2014.
2. Oien KA, Evans TR. Raising the profile of cancer of unknown primary. J Clin Oncol. Sep 20 2008; 26(27):4373-4375. PMID 18802148
3. Horlings HM, van Laar RK, Kerst JM, et al. Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinomas of unknown primary. J Clin Oncol. Sep 20 2008; 26(27):4435-4441. PMID 18802156
4. Ma XJ, Patel R, Wang X, et al. Molecular classification of human cancers using a 92-gene real-time quantitative polymerase chain reaction assay. Arch Pathol Lab Med. Apr 2006; 130(4):465-473. PMID 16594740
5. Ramaswamy S, Tamayo P, Rifkin R, et al. Multiclass cancer diagnosis using tumor gene expression signatures. Proc Natl Acad Sci U S A. Dec 18 2001; 98(26):15149-15154. PMID 11742071
6. Su AI, Welsh JB, Sapinoso LM, et al. Molecular classification of human carcinomas by use of gene expression signatures. Cancer Res. Oct 15 2001; 61(20):7388-7393. PMID 11606367
7. Tothill RW, Kowalczyk A, Rischin D, et al. An expression-based site of origin diagnostic method designed for clinical application to cancer of unknown origin. Cancer Res. May 15, 2005; 65(10):4031-4040. PMID 15899792

8. Bloom G, Yang IV, Boulware D, et al. Multi-platform, multi-site, microarray-based human tumor classification. Am J Pathol. Jan 2004; 164(1):9-16. PMID 14695313
9. Agwa E, Ma PC. Overview of various techniques/platforms with critical evaluation of each. Curr Treat Options Oncol. Dec 2013; 14(4):623-633. PMID 24243164
10. Dumur CI, Lyons-Weiler M, Sciulli C, et al. Interlaboratory performance of a microarray-based gene expression test to determine tissue of origin in poorly differentiated and undifferentiated cancers. J Mol Diagn. Jan 2008; 10(1):67-77. PMID 18083688
11. U.S. Food and Drug Administration. Decision summary: Pathwork Tissue of Origin Test Kit-FFPE, 06/08/2010. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=32236. Accessed October 20, 2014.
12. Grenert JP, Smith A, Ruan W, Pillai R, Wu AH. Gene expression profiling from formalin-fixed, paraffin-embedded tissue for tumor diagnosis. Clin Chim Acta. Jul 15 2011; 412(15-16):1462-1464. PMID 21497155
13. Pillai R, Deeter R, Rigl CT, et al. Validation and reproducibility of a microarray-based gene expression test for tumor identification in formalin-fixed, paraffin-embedded specimens. J Mol Diagn. Jan 2011; 13(1):48-56. PMID 21227394
14. Monzon FA, Lyons-Weiler M, Buturovic LJ, et al. Multicenter validation of a 1,550-gene expression profile for identification of tumor tissue of origin. J Clin Oncol. May 20, 2009; 27(15):2503-2508. PMID 19332734
15. Azueta A, Maiques O, Velasco A, et al. Gene expression microarray-based assay to determine tumor site of origin in a series of metastatic tumors to the ovary and peritoneal carcinomatosis of suspected gynecologic origin. Hum Pathol. Jan 2013; 44(1):20-28. PMID 22939961
16. Handorf CR, Kulkarni A, Grenert JP, et al. A multicenter study directly comparing the diagnostic accuracy of gene expression profiling and immunohistochemistry for primary site identification in metastatic tumors. Am J Surg Pathol. Jul 2013; 37(7):1067-1075. PMID 23648464
17. Nystrom SJ, Hornberger JC, Varadhachary GR, et al. Clinical utility of gene-expression profiling for tumor-site origin in patients with metastatic or poorly differentiated cancer: impact on diagnosis, treatment, and survival. Oncotarget. Jun 2012; 3(6):620-628. PMID 22689213
18. Erlander MG, Ma XJ, Kesty NC, Bao L, Salunga R, Schnabel CA. Performance and clinical evaluation of the 92-gene real-time PCR assay for tumor classification. J Mol Diagn. Sep 2011; 13(5):493-503. PMID 21708287
19. Kerr SE, Schnabel CA, Sullivan PS, et al. Multisite validation study to determine performance characteristics of a 92-gene molecular cancer classifier. Clin Cancer Res. Jul 15 2012; 18(14):3952-3960. PMID 22648269
20. Kerr SE, Schnabel CA, Sullivan PS, et al. A 92-gene cancer classifier predicts the site of origin for neuroendocrine tumors. Mod Pathol. Jan 2014; 27(1):44-54. PMID 23846576
21. Greco FA, Lennington WJ, Spigel DR, Hainsworth JD. Molecular profiling diagnosis in unknown primary cancer: accuracy and ability to complement standard pathology. J Natl Cancer Inst. Jun 5 2013; 105(11):782-790. PMID 23641043
22. Greco FA, Lennington WJ, Spigel DR, Hainsworth JD. Poorly differentiated neoplasms of unknown primary site: diagnostic usefulness of a molecular cancer classifier assay. Mol Diagn Ther. Apr 2015; 19(2):91-97. PMID 25758902
23. 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 Unknown Primary Site: A Prospective Trial of the Sarah Cannon Research Institute. J Clin Oncol. January 10, 2013; 31(2):217-223.
24. Varadhachary GR, Raber MN. Cancer of unknown primary site. N Engl J Med. Aug 21 2014; 371(8):757-765. PMID 25140961
25. Chajut A, Rosenwald S, Edmonston TB. Development and validation of a second generation microRNA-based assay for diagnosing tumor tissue origin. Cancer Res. 2011; 71(8 Suppl):1148.
26. Meiri E, Mueller WC, Rosenwald S, et al. A second-generation microRNA-based assay for diagnosing tumor tissue origin. Oncologist. 2012; 17(6):801-812. PMID 22618571
27. Mueller WC, Spector Y, Edmonston TB, et al. Accurate classification of metastatic brain tumors using a novel microRNA-based test. Oncologist. 2011; 16(2):165-174. PMID 21273512

28. Rosenfeld N, Aharonov R, Meiri E, et al. MicroRNAs accurately identify cancer tissue origin. Nat Biotechnol. Apr 2008; 26(4):462-469. PMID 18362881
29. Rosenwald S, Gilad S, Benjamin S, et al. Validation of a microRNA-based qRT-PCR test for accurate identification of tumor tissue origin. Mod Pathol. Jun 2010; 23(6):814-823. PMID 20348879
30. Meleth S, Whitehead N, Evans TS, Lux L. Technology Assessment on Genetic Testing or Molecular Pathology Testing of Cancers with Unknown Primary Site to Determine Origin. AHRQ Technology Assessments. Rockville (MD). 2013. PMID 25855837
31. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: occult primary (cancer of unknown primary [CUP]), version 1.2015. http://www.nccn.org/professionals/physician_gls/pdf/occult.pdf. Accessed October 20, 2014.
32. National Institute for Health and Clinical Excellence (NICE). Diagnosis and management of metastatic malignant disease of unknown primary origin (clinical guideline no. 104). London (UK): 2010. http://guidance.nice.org.uk/CG104. Accessed October 20, 2014.
33. Fizazi K, Greco FA, Pavlidis N, Group EGW. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. Sep 2015; 26 Suppl 5:v133-138. PMID
34. Fizazi K, Greco FA, Pavlidis N, Pentheroudakis G. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. Sep 2011; 22 Suppl 6:vi64-68. PMID 21908507
35. Noridian Healthcare Solutions, LLC, (Jurisdiction-California-Entire State, American Samoa, Guam, Hawaii, Northern Mariana Islands, Nevada) (Jurisdiction-Montana, North Dakota, South Dakota, Utah, Wyoming, Arizona, Idaho, Alaska, Oregon, Washington) Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35160), Revision Effective Date for services performed on or after 04/21/2016.