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Medical Policy Manual

Topic: Microarray-Based Gene Expression Testing for Cancers of Unknown Primary

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Section: Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The current success rate of the diagnostic workup of a cancer of unknown primary is 20%–30%, including consideration of clinical, radiologic, and extensive histopathologic methods.[1] 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. The benefit of identifying cancers of unknown primary is to identify appropriate cancer-specific treatment, expected outcome and prognosis.

The molecular classification of cancers is based on the premise that, despite different degrees of loss of differentiation, tumors retain sufficient gene expression "signatures" related 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.

One such microarray technology is the ResponseDX®: Tissue of Origin Test (Response Genetics, Inc., Los Angeles, CA), formerly known as the Pathwork® Tissue of Origin Test.. The test measures the expression of more than 1,500 genes and compares the similarity of the gene expression profile of a cancer of unknown primary 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 gene expression profile of the specimen to the profile of the 15 known tumors in the database. Scores range from 0 (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 5 and 30, the test result is considered indeterminate, and a similarity score of less than 5 rules out that tissue type as the likely origin. The test was developed by Pathwork Diagnostics, but was later purchased by Response Genetics, Inc.

MiReview® 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 MiReview test utilizes 48 panel markers used to detect 22 tumor types in a known database of 336 tumors with a range of 1 to 49 tumors per type. The results from the test provide a tumor of origin but may list multiple possibilities.. A second generation test, the Rosetta Cancer Origin Test™ (formerly miReview® 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 7 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.[2] 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 cancer of unknown primary (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 5 reference genes for normalization) are used to detect 27 tumor types in a known database of 578 tumors with a range of 5 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, the ResponseDX®: Tissue of Origin Test (Response Genetics, Inc., Los Angeles, CA), formerly known as the Pathwork® Tissue of Origin Test, was cleared with limitations* for marketing by the 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 pathological practice. The database contains examples of RNA expression patterns for fifteen 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-Hodgkins lymphoma (not otherwise specified), and soft tissue sarcoma (not otherwise specified). The ResponseDX®: 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:[3]

The ResponseDX®: Tissue of Origin Test is not intended to establish the origin of tumors that cannot be diagnosed according to current clinical and pathological 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 pathological practice, nor to predict disease course, or survival or treatment efficacy, nor to distinguish primary from metastatic tumor. Tumor types not in the ResponseDX®: 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" (Pathwork Diagnostics) 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. As of late 2013, the Tissue of Origin Test is distributed by Response Genetics, Inc.

To date, the CancerTypeID®, miReview® or Rosetta Cancer Origin Test™ tests have not been submitted to the FDA for approval.

MEDICAL POLICY CRITERIA

Gene expression profiling is considered **investigational** to evaluate the site of origin of a tumor of unknown primary, and to distinguish a primary from a metastatic tumor. Gene expression tests for this indication include, but are not limited to, the ResponseDX®:Tissue of Origin Test, the ResponseDX®:Tissue of Origin test kit-FFPE, CancerTypeID®, miReview®, and Rosetta Cancer Origin Test™.

SCIENTIFIC EVIDENCE

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

Literature Appraisal

ResponseDX®: Tissue of Origin Test and Rosetta Cancer Origin™

Current studies regarding the ResponseDX®: Tissue of Origin Test and Rosetta Cancer Origin tests primarily compare the diagnostic accuracy of the test to other diagnostic methods, such as pathology or immunohistochemistry (IHC) testing.[4-6] There are no published clinical trials that provide direct evidence of the clinical utility of these tests. No prospective studies have been published which compare patient management and tumor site-specific therapy based on gene expression profiling to direct patient management with current clinical, radiologic and histopathologic practices. Without such comparisons, it is not possible to determine how use of the test affects clinical practice and clinical health outcomes for patients diagnosed through the use of these tests.

CancerTypeID®

In 2013, Hainsworth and colleagues conducted a multi-site prospective case-series of the 92-gene CancerTypeID assay[7]. The molecular profiling assay predicted a tissue of origin in 247 (98%) of 252 patients. One-hundred nineteen assay predictions were made with ≥80% similarity score and the rest were below 80% probability. Twenty-nine patients did not remain on study due to decreasing performance, brain metastases, or patient and physician decision. Of the remaining 223 patients, 194 (87%) received assay-directed chemotherapy, and 29 received standard empiric therapy. The median overall survival of the 194 patients receiving assay-directed chemotherapy was12.5 months, which was found to be within the *a priori*-specified improvement target of 30% compared with historical trial data on 396 performance-matched CUP patients receiving standard empiric therapy at the same center. This study had several methodological limitations, including lack of randomization, limited sample size, no control group within the study.

Clinical Practice Guidelines

National Comprehensive Cancer Network NCCN

The NCCN guidelines for the workup of an occult primary malignancy address the use of molecular methods in the classification of tumors. They conclude that there is insufficient data to confirm whether gene expression profiling can be used in choosing treatment options which would improve the prognosis of patients with occult primary cancers. Therefore the panel does not recommend the testing as a part of routine evaluation of a cancer of unknown primary origin.[8]

Summary

There is insufficient data on how microarray-based gene expression testing alters clinical practice and clinical health outcomes (clinical utility) in patients with cancers of unknown primary. Additionally, there are no evidence-based clinical practice guidelines which recommend the use of these tests to identify cancers of unknown primary. Therefore, microarray-based gene expression testing is considered investigational to identify cancers of unknown primary.

REFERENCES

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identification in metastatic tumors. *Am J Surg Pathol*. 2013 Jul;37(7):1067-75. PMID: 23648464
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8. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Occult Primary. v.1.2014. [cited 01/24/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/occult.pdf

CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64

CODES	NUMBER	DESCRIPTION
CPT	81479	Unlisted molecular pathology procedure
	81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
	84999	Unlisted chemistry procedure
HCPCS	None	