

FEP 2.04.54 Gene Expression–Based Assays for Cancers of Unknown Primary

Effective Date: July 15, 2018

Related Policies: None

Gene Expression–Based Assays for Cancers of Unknown Primary 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.

FDA REGULATORY STATUS

In 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 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.

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

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RosettaGX Cancer Origin™; Rosetta Genomics, Philadelphia, PA) are available under the auspices of the Clinical Laboratory Improvement Amendments. Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

POLICY STATEMENT

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

The Human Genome Variation Society 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). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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

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.

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BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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 CUP who receive GEP, the evidence includes studies of clinical validity, and limited evidence on potential clinical utility. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. Of the 3 commercially available tests reviewed, one has been cleared by the 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, 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 who had CUP with 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.1.2018) address the use of molecular methods to classify tumors.⁷ 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... 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 determining 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 cancer classifier assays (gene signature profiling) at this time for the identification of tissue of origin as standard management in the diagnostic workup of patients with CUP [cancer of unknown primary]. -Furthermore, the panel believes that neither IHC, a diagnostic tool in widespread use, nor GEP should be used indiscriminately."

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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 (GEP) to identify primary tumors in patients with cancers of unknown primary.³⁰ This recommendation was based on “limited evidence that gene-expression based profiling changes the management of patients with CUP and no evidence of improvement in outcome.” The guidance included a research recommendation for trials to assess the clinical utility of GEP.

European Society of Medical Oncology

The 2015 guidelines from the European Society of Medical Oncology stated that, as relates to use of GEP assays to identify tissue of origin in patients with cancer of unknown primary, “their impact on patient outcome via administration of primary site specific therapy remains questionable and unproven in randomized trials” (level of evidence: IV based on “retrospective cohort studies or case–control studies”; grade of recommendation C: “insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages.”)³¹ Rather, “Immunohistochemistry should be applied meticulously in order to identify the tissue of origin and to exclude chemosensitive and potentially curable tumors (ie, lymphomas and germ cell tumors).”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

A 2013 technology assessment was commissioned by Centers for Medicare & Medicaid for consideration by the MEDCAC panel.³² 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?”)³³

There are no national Medicare coverage decisions for these tests, but local Medicare coverage decisions for all 3 tests have found them to be “reasonable and necessary.” In 2011, Palmetto GBA, 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.

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POLICY HISTORY

Date	Action	Description
September 2012	New	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.
March 2013	Update Policy	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.
March 2014	Update Policy	Policy updated with literature review; references 14, 15, 17, 25, and 29 updated. No change to policy statement.
March 2015	Update Policy	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.
June 2017	Update Policy	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.
June 2018	Update Policy	Policy updated with literature review through January 8, 2018; no references added. Policy statement unchanged.

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