FEP Medical Policy Manual

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

Annual Effective Policy Date: July 1, 2024

Original Policy Date: September 2012

Related Policies:

None

Gene Expression-Based Assays for Cancers of Unknown Primary

Description

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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.

OBJECTIVE

The objective of this evidence review is to evaluate whether gene expression profiling in patients with cancers of unknown primary improves the net health outcome compared with standard of care management based on tumor type and probable site of origin.

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

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

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.

FDA REGULATORY STATUS

In 2008, the PathWork Tissue of Origin Test™ (Response Genetics was acquired by Cancer Genetics, Cancer Genetics merged with StemoniX in 2020 and was renamed Vyant Bio, Inc. in 2021) 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.

RATIONALE

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, 1 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 1 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 2 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. 1.2024) address the use of molecular methods to classify tumors.[26,] Gene sequencing to predict tissue of origin is not recommended. 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. Both methodologies offer a similar range of accuracy in tumor classification (approximately 75%). 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 on diagnosis and management of malignant disease of unknown primary origin from the National Institute for Health and Care Excellence (NICE) was updated in 2023. In the 2023 update, NICE withdrew recommendations on gene-expression-based profiling and added a link to the NHS Genomic Medicine Service"s national genomic test directory..[27,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

A 2013 technology assessment was commission by Centers for Medicare & Medicaid for consideration by the MEDCAC panel.[28,] 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?")[29,]

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2012	New 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.
March 2013	Replace 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	Replace policy	Policy updated with literature review; references 14, 15, 17, 25, and 29 updated. No change to policy statement
March 2015	Replace 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	Replace 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	Replace policy	Policy updated with literature review through January 8, 2018; no references added. Policy statement unchanged.
June 2019	Replace policy	Policy updated with literature review through January 9, 2019; no references added. Policy statement unchanged.
June 2020	Replace policy	Policy updated with literature review through February 21, 2020; references added. Policy statement unchanged.
June 2021	Replace policy	Policy updated with literature review though February 13, 2021; no references added. Policy statement unchanged.
June 2022	Replace policy	Policy updated with literature review through January 24, 2022; no references added. Policy statement unchanged.
June 2023	Replace policy	Policy updated with literature review through February 7, 2023; no references added. Policy statement unchanged.
June 2024	Replace policy	Policy updated with literature review through January 16, 2024; no references added. Policy statement unchanged.