



Cancer of Unknown Primary (Identification of Origin)

Test code: 16107X

Clinical Use

- Identify site of origin in cancer of unknown primary (CUP)
- Establish prognosis
- Determine appropriate therapy

Clinical Background

Approximately 5% of newly diagnosed cancers are metastases from an unknown site of origin.¹ These cancers are a heterogeneous group of malignancies classified as well- to moderately differentiated adenocarcinomas (50% to 60%) or as poorly differentiated adenocarcinomas or carcinomas (30% to 40%). Fewer than 14% are squamous cell carcinomas or undifferentiated malignancies.¹ Lung and pancreatic tumors are the most common sites of origin, with metastases originating less often from colorectal, stomach, breast, ovarian, and prostate tumors.²

CUP, cancer of unknown primary, generally has a poor prognosis with a median survival of 2 to 10 months.² Classification of a CUP into 1 of several subsets with known response to a specific treatment regimen can lead to improved survival.²⁻⁴ Such classification is based on the histopathology and anatomic localization of the tumor.^{2,3} When possible, identifying the primary tumor site provides prognostic information and helps with selection of tumor-specific therapy, leading to improved survival. For example, in a study of 879 consecutive patients with suspected CUP, survival duration was increased when the primary tumor site was identified and treatment was directed toward each primary tumor type.⁵

Conventional diagnostic approaches for identifying the primary tumor site include a detailed medical history and physical examination, a basic laboratory work-up, tumor histology and immunohistochemistry, and imaging studies.^{2,6} However, such techniques are successful in only 20% to 30% of cases.⁶ Molecular approaches such as examination of gene expression profiles can increase the frequency of primary tumor site identification.^{6,7} Gene expression profiles based on mRNA patterns differ among primary tumor sites; the site of origin of a CUP can be predicted by comparing an unknown tumor profile against a database of reference gene expression profiles from known tumor sites.

Quest Diagnostics Nichols Institute uses gene expression profiling of CUP tissue to determine the primary tumor site. Using the patient's specimen, gene expression data

are generated for 92 genes. The patient's gene expression profile is then compared to a reference database comprising gene expression profiles from 39 known tumor types.⁸ Based on this comparison, the most likely site of origin is determined. To independently validate the assay, 58 specimens with known tumor type were tested. Assay results agreed with the known site of tumor origin in 45/55 cases (82%); results were indeterminate in 3 samples (5%).⁹

Individuals Suitable for Testing

- Patients with cancer of unknown primary tumor site

Specimen Requirements

Formalin-fixed, paraffin-embedded tumor tissue. Ship at room temperature.

Alternatively, submit fresh frozen tissue samples (–70°C or colder).

Provide pathology report or suspected pathological diagnosis.

Method

- Microscopic examination of sample to ensure >50% tumor tissue; laser capture microdissection will be used if <50%
- Gene expression profiling:
 - Reverse-transcription of poly A mRNA into cDNA followed by purification
 - In vitro transcription of cDNA followed by RNA purification and cDNA biosynthesis
 - Quantitative real-time polymerase chain reaction (PCR) analysis of cDNA from 92 genes; data from 5 of these genes used to normalize fluorescent signal
 - Comparison of test sample gene expression data to gene expression profiles from 39 known tumor types from 571 samples using k-nearest neighbor analysis
- Results reported as most likely site(s) of tumor origin with an associated confidence value
- CPT code*: 83891, 83902, 83912, 83898 x92

Interpretive Information

The specified tumor site with the highest confidence value is most likely to be the original site of the tumor; tumor sites with lower confidence values are less likely to be the primary tumor site. Confidence values are based on how close the patient's tumor gene expression profile matches that of known tumor types.

This assay does not distinguish primary tumors from metastases. The results should be interpreted in light of other relevant clinical and laboratory findings.

References

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7. Dennis JL, Vass JK, Wit EC, et al. Identification from public data of molecular markers of adenocarcinoma characteristic of the site of origin. *Cancer Res.* 2002;62:5999-6005.
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9. Data on file at Quest Diagnostics Nichols Institute.

*The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payor being billed.

This test was developed and its performance characteristics determined by Quest Diagnostics Nichols Institute. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.

Polymerase chain reaction (PCR) is performed pursuant to a license agreement with Roche Molecular Systems, Inc.

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