Tissue of Origin Testing for Cancer of Unknown Primary

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
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<td>Miscellaneous Tissue of Origin Test</td>
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<td>CancerTYPE ID</td>
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What is cancer of unknown primary testing

Definition

In order to determine the most effective treatment regimen for a patient with cancer it is important to identify the cancer cell type.¹

- When a cancer is found in one or more metastatic sites but the primary site is not known, it is called a cancer of unknown primary (CUP) or an occult primary cancer.² This happens in a small portion of cancers.
- The most commonly used techniques to identify tissue of origin (TOO) for CUP include light microscopy, immunohistochemistry (IHC) staining and computed tomography (CT) or positron emission tomography (PET) imaging.¹
- With advances in technology, some laboratory tests utilize gene expression profiling or other molecular techniques in cancer cells. Ramaswamy et al. found that a cancer-intrinsic gene expression pattern distinguished primary from metastatic adenocarcinomas.³ By comparing the pattern of gene expression in the CUP sample to the patterns seen with other known types of cancer, a CUP may be identified as belonging to a particular cancer type.
Test information
A number of different companies and approaches are being utilized to diagnose metastatic neoplasms for patients with CUP, typically using gene expression analysis.

Guidelines and evidence
- According to 2019 NCCN guidelines for CUP (occult primary), gene signature profiling for tissue of origin is not recommended for standard management at this time. The panel states the following:
  - "As noted, outcomes data are not currently available to recommend routine use of molecular profiling in the working of CUP."\(^4\)
  - "the clinical benefit that might be derived from the use of these molecular assays, if any, remains to be determined."\(^4\)
  - Use of molecular testing for CUP is considered a category 3 recommendation by NCCN.
- In systematic reviews of cancer of unknown primary site, gene-profiling diagnosis was noted to have high sensitivity, but additional prospective studies were deemed necessary to establish whether patients' outcomes are improved by its clinical use.\(^5,6\)

Criteria
This test is considered investigational and/or experimental.
- Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
- In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References
February 20, 2013. Available at: 


