Tissue of Origin Testing for Cancer of Unknown Primary

MOL.TS.228.A
v2.0.2025

Introduction

Tissue of origin testing for cancer of unknown primary is addressed by this guideline.

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.

Procedures addressed by this guideline	Procedure codes
Oncology (tissue of origin), microarray gene expression profiling of greater than 2000 genes (e.g. tissue of origin testing)	81504
Oncology (tumor of unknown origin), mRNA, gene expression profiling of real-time RT-PCR of 92 genes to classify tumor into main cancer type and subtype (e.g. CancerTYPE ID)	81540
Unlisted molecular testing for tumor of unknown origin	81479
Unlisted multianalyte assay for tumor of unknown origin	81599

Criteria

Introduction

Requests for tissue of origin testing for cancer of unknown primary are reviewed using the following criteria.

This test is considered Experimental, Investigational, or Unproven.

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- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

What is cancer of unknown primary testing?

In order to determine the most effective treatment regimen for an individual 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.[1,3] However, conventional methods have had poor success.[4,5]
- With advances in technology, some laboratory tests utilize gene expression profiling (GEP) or other molecular techniques in cancer cells. Ramaswamy et al. found that a cancer-intrinsic gene expression pattern distinguished primary from metastatic adenocarcinomas.[6] 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. Survival, quality of life (QOL), and/or disease symptoms may improve in some cases if the site and type of primary origin can be accurately detected and appropriate therapy administered early in the disease course.[7,8]

Test information

Introduction

A number of different companies and approaches are being utilized to diagnose metastatic neoplasms for individuals with CUP, typically using gene expression analysis.

A representative example of a tissue-of-origin test, CancerTYPE ID (Hologic, Inc), is a gene expression test designed to identify the most likely tissue of origin from 50 tumor

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types in individuals with cancer of unknown primary.[9] "CancerTYPE ID uses real-time RT-PCR to measure the expression of 92-genes in the patient's tumor and classifies the tumor by matching the gene expression pattern to a database of over 2,000 known tumor types and subtypes...The test reports a molecular diagnosis of the cancer type with the highest probability match, as well as a list of tumor types that may be ruled out with 95% confidence."[9]

Guidelines and evidence

European Society for Medical Oncology

The European Society for Medical Oncology (ESMO, 2023) Clinical Practice Guideline for the diagnosis, treatment and follow-up of cancer of unknown primary stated the following:[10]

- "Despite a promising pilot study, two randomised trials failed to demonstrate superiority of gene expression profiling-based 'site-specific' therapy over standard empiric [(neo)adjuvant chemotherapy] with either carboplatine—paclitaxel or cisplatine—gemcitabine, respectively. Consequentially, no recommendation for the use of gene expression profiling-based 'site-directed' therapy can currently be provided."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network Guidelines in Oncology: Occult Primary (NCCN, 2024) stated the following regarding tissue of origin testing:[11]

- "...the Panel does not currently recommend use of gene sequencing to predict tissue of origin."
- "...the clinical benefit of using molecular profiling to guide treatment decisions in CUP remains to be determined."
- "Currently there is no evidence of improved outcomes with the use of site-specific therapy guided by molecular testing in patients with CUP."
- "While there may be a diagnostic benefit to GEP, a clinical benefit has not been demonstrated. Consequently, the panel does not currently recommend use of gene sequencing to predict tissue of origin. Until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of IHC and GEP on a case-by-case basis, with the best possible individualized patient outcome in mind."

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE, 2023) clinical guideline for metastatic malignant disease of unknown primary origin stated that further research

is required to determine whether gene-expression-based profiling "could be beneficial addition to standard management in CUP."[12]

Select Relevant Publications

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 outcomes for individual's with cancer are improved by its clinical use.[1,13-22]

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for tissue of origin testing for cancer of unknown primary will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[23] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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