Local Coverage Determination (LCD) for Molecular Profiling for Unknown Primary Cancers (UPC) (L31628)

Contractor Information

Contractor Name	Contractor Number	Contractor Type
Palmetto GBA	01192	MAC - Part B

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LCD Information

Document Information

LCD ID Number
L31628

LCD Title
Molecular Profiling for Unknown Primary Cancers (UPC)

Contractor's Determination Number
J1B-11-0001-L

AMA CPT/ADA CDT Copyright Statement

Primary Geographic Jurisdiction
California - Southern

Oversight Region
Region X

Original Determination Effective Date
For services performed on or after 07/25/2011

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CMS National Coverage Policy
Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or service that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of malformed body member."

Title XVIII of the Social Security ACT (SSA), §1862(a)(7) and 42 Code of Federal Regulations, §411,15, exclude routine physical examinations.

Title XVIII of the Social Security Act (SSA), §1833(e), prohibit Medicare payment for any claim lacking the necessary documentation to process the claim.

42 CFR §410.32(d)(3)indicates diagnostic tests are payable only when the physician who is treating the beneficiary for specific medical problem and who uses the results in such treatment.

Title XVIII of the Social Security Act (SSA) §1862(a)(1)(D), Investigational or Experimental.

CMS Manual System, Pub. 100-08, *Medicare Program Integrity Manual,* Chapter 3, §3.4.1.1.G, states that contractors may require ICD-9 diagnosis codes to be submitted by providers, with every claim for a targeted service if such a requirement appears in an LCD for that service.

CMS Manual System, Pub. 100-08, *Medicare Program Integrity Manual,* Chapter 3, §3.4.1.2, states that the billing provider is liable for charges, if at the request of the contractor, the ordering provider does not provide adequate documentation to support the medical necessity of the test.

CMS Manual System, Pub. 100-02, *Medicare Benefit Policy,* Chapter 15, §§ 80.1, 80.1.1, 80.1.2, laboratory services must meet applicable requirements of CLIA.

Indications and Limitations of Coverage and/or Medical Necessity
The ability to identify a primary tumor site has become increasingly important with the growing use of chemotherapy regimens and targeted agents directed against specific tumor types. With advances in tumor gene-expression profiling, such as real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assays and microarray techniques, it is possible to compare cancers of unknown primary (UPC) to well characterized primary tumor profiles.

UPCs account for 3-5% of cancer diagnoses per year. The large majority of UPCs are poorly differentiated or undifferentiated carcinomas occasionally confused with other lineages such as lymphoma, sarcoma and melanoma. When the initial diagnostic evaluation that includes history and physical exam, appropriate blood and imaging studies, tumor evaluation by pathology, including immunohistochemical (IHC) marker studies, and consultation with pathologists, radiologists and oncologists, does not define the site of origin, the diagnosis of UPC is established (6).

The IHC workup depends on the most likely suspected tissues based on morphology, sex and biopsy site. Despite the development of more precise IHC stains, there is no single IHC panel or standard of care for tissue determination for metastatic tumors. For many cases there is often uncertainty even after a full evaluation. The success rate in identifying the origin of metastatic tumors is roughly 67% overall (2). For patients presenting with UPC, the success rate drops to 25% even after an exhaustive workup (8).

Studies demonstrate the median survival rate for patients with an unidentified primary sites range from 2-3 months to 6-10 months in clinical studies of unselected patients with UPC. Current studies suggest appropriate tissue of origin identification with UPC results in improved treatment outcomes (26, 27, 30).

Gene expression profiling is an important new tool in the diagnostic armamentarium for pathologists and oncologists. Gene profiling assays, specifically bioTheranostic's CancerTYPE ID (CTID) and Pathwork's Tissue of Origin (TOO), may be useful to identify poorly-differentiated or undifferentiated malignant neoplasms or exclude multiple differential diagnoses.

Pathwork® Tissue of Origin Test (TOO); (Pathwork Diagnostic, Inc., Redwood City, CA)

The TOO test is a microarray-based gene expression assay designed to determine the similarity of unknown or unresolved tumors to cancers from 1 of 15 known tumors of origin. The test uses proprietary normalization and classification algorithms and a companion high-density oligonucleotide microarray to measure the expression of 2029 gene probe markers. The assay compares the molecular similarity of each tumor's expression pattern to 15 distinctive patterns from the different tissue types covered by the test. The tumor tissue types represented are bladder, breast, colorectal, gastric, hepatocellular, kidney, non-small cell lung, ovarian, pancreatic, prostate, thyroid carcinomas, melanoma, testicular germ cell tumor, non-Hodgkin's lymphoma and sarcoma. For each specimen, the algorithm reduces the expression data into 15 separate similarity scores that range from 0-100.

In 2003 a microarray platform comparison study showed that gene expression profiles were not reproducible when using various commercial microarray platforms (28). In 2005, these concerns were addressed by a consortium of academic institutions, industry and the FDA. The consortium findings showed significant improvement between different microarray platforms and high reproducibility in gene expression data with the use of standardized protocols and array platforms (16). To overcome reported variability in gene expression measurements, developers of the TOO assay used gene expression profiles from 5539 human tissue specimens to develop a 121-gene standardization algorithm (3). Subsequently, a classification algorithm from gene expression profiles of 2039 tumors comprising 15 tissue types and 58 different morphologic features was developed. The training set included both primary and metastatic tumors and well-differentiated to undifferentiated tumors.

Four laboratories using archival frozen tissue from 60 poorly to undifferentiated primary and metastatic tumors evaluated the analytical performance and reproducibility of the frozen tissue test. Although this study was not designed to provide sufficient statistical power to evaluate clinical performance, there was good reproducibility in the standardized expression values, similarity score and final tissue diagnoses between sites (3). Average percentage agreement between results and the reference diagnosis was 86.7%.

A multicenter validation study with an independent sample set of 547 samples, consisting of a minimum of 25 specimens for each of the 15 tissues in the test, showed an overall accuracy of 87.8% and overall specificity of 99.4% (20). Wu et al reported that the TOO test accurately predicted the diagnosis in 12 of 13 metastatic brain tumors. Although this study did not have sufficient statistical power to evaluate clinical performance, there was 92.3% accuracy with known primary site diagnoses (31).

A retrospective study of 21 archival frozen tumor specimens from patients diagnosed with UPC gave a positive result for a single tissue in 16 (76%) specimens. The specimens had been archived between 1998 and 2006. The TOO test was indeterminate in 5 cases (24%) (21).

Array technologies have traditionally required large amounts of fresh or frozen tissue, which is impractical in routine clinical use. Because nucleic acids are well known to undergo chemical degradation, fragmentation, cross-linking with proteins, and methylation during fixation and storage, the degraded RNA typically found in formalin-fixed paraffin-embedded (FFPE) tissue has been considered unsuitable for microarray analysis. However, several studies have shown that microarray tests can be performed on FFPE specimens for measurement of short non-coding microRNAs and for quantification of thousands of diverse mRNA transcripts (13, 27, 5, 17).

The development of a FFPE-based TOO test was a major technological breakthrough because the method procured high-quality microarray data from nearly 80% of FFPE specimens (25). A standardization algorithm, similar to that used for frozen specimens, was optimized for FFPE samples and allowed reproducibility across microarrays, laboratories, operators and testing times. A tumor classification algorithm using machine learning and cross-validation was developed from 2000 gene expression data files from frozen tissues and 104 data files from FFPE derived RNA. The classification algorithm for the FFPE version of the test used different but overlapping sets of genes compared to the frozen version of the test.

Because a different classification algorithm was used for the FFPE TOO test, internal validation was performed by Pathwork on a completely independent set of 462 poorly differentiated, undifferentiated, and metastatic human tumor FFPE samples. This blinded, multisite study yielded an overall agreement with known diagnoses of 88.5% (25). Performance for both metastatic tumor specimens showed 91% agreement, while poorly differentiated primary tumor specimens showed 87% agreement. These findings are in marked contrast to a recent meta-analysis of four large studies, which showed that IHC correctly identified the primary site in only 66% of metastatic tumors (1).

Pillai's study demonstrates that microarray analysis of typical FFPE specimens is feasible and can provide results that are accurate and reproducible. The validation study consisted of at least 25 specimens per tissue type which allows confidence in the overall accuracy for both rule-in and rule-out tissue of origin results. In addition to the "rule-in" (positive test) results, an average of 12 tissue types per specimen could be "ruled-out" with > 99% probability. Furthermore, the multisite reproducibility study showed 89.3% concordance between laboratories (25). In 2010, the FDA cleared the FFPE version of this test largely based on the Pillai data.

For the FFPE TOO test, the highest similarity score that is 20 or more is considered evidence that the specific tissue is present in the specimen. A similarity score of less than 5 rules out a particular tumor type. A score between 5 and 20 is classified as indeterminate. Note, the classification algorithms for the frozen and FFPE TOO tests are different. The thresholds for a "determinate" similarity score were set independently for each test based on both the training/test set data and the results of the validation studies for each test. Only the FFPE TOO assay is commercially available.

There is a growing body of evidence that the TOO test provides valuable information to medical practice. A published abstract noted that the TOO test predicted the site of origin in 43 of 45 UPC tissue biopsies that contained adequate amount of tumor. The authors noted that the TOO predictions were consistent with clinical features, histology and response to empiric therapy (9).

Another published abstract noted that 64% of 284 consecutive study cases had non-specific diagnoses of primary site. The TOO test resulted in either a change from non-specific to specific site, or a change from one primary site to another in 81% of cases. For 15% of cases, the TOO test confirmed the submitted diagnosis. It also suggested that first line chemotherapy treatment would change for 63% of 284 consecutive CUP patients based on TOO test results (15).

A registry study of 111 cases that was presented at the 2011 ASCO GI conference showed that the TOO test result changed the primary site diagnosis 54% of the time, that the test results confirmed the diagnosis 34% of the time, and that the test results changed treatment (chemotherapy, radiation and surgery) 65% of the time (12).

bioTheranostics CancerTYPE ID® (CTID) (bioTheranostics, Inc. San Diego, CA)

CTID, a laboratory developed test (LDT), is an RT-PCR 92-gene assay. The first generation of the test was reported to classify 39 different tumor types and 64 tumor subtypes (18). In brief, this assay consists of either manual tumor dissection or laser microdissection of FFPE tumor from tumor tissue affixed to microscope slides. After overnight incubation with proteinase K, the RNA is extracted, amplified and analyzed for the expression of 87 cancer-associated genes and five reference genes using TaqMan real-time reverse transcriptase-polymerase chain reaction (RT-PCR). Tumor prediction is made from a proprietary algorithm using the test profile compared to each of the 39 tumor types in the reference classification database.

The test was developed using gene expression microarrays of 22,000 genes to generate profiles from 466 frozen tumors and 112 FFPE tumor specimens. Seventy-five percent (75%) of the specimens were primary tumors; the remaining tumors were metastatic. From approximately 1000 informative genes with an overall accuracy of 82%, a bioinformatic approach was utilized to derive more compact gene sets that demonstrated comparable performance. Eighty-seven (87) classification and 5 reference genes were ultimately selected to construct the 92-gene assay for tumor classification (18).

The 92-gene assay was evaluated with 119 FFPE tumor samples representing 30 tumor classes (18). The study authors report an overall accuracy of 82%. Concerns have been expressed because the independent sample set had only 119 tumors to represent 30 tumor classe. Eighteen (18) of these 30 tumor classes were represented by 3 samples or less. The relatively small sample size and class representation were suboptimal (26, 14). Because cancer classifiers quantify the molecular similarity of the gene expression profile from a sample tissue to a reference database of known tumor types, the scope of the reference database must include an ample number of samples within each class to represent the inherent cellular heterogeneity of tumors. Also, there has been no external validation of this assay.

The small sample size and class representation noted above is addressed in an expanded, second generation version of the CTID assay that classifies 30 main tumor types and 54 histological subtypes. Increased tissue coverage was achieved through expansion of a reference tumor database containing 2206 specimens with a median of 62 samples per main tumor type. The classification algorithm is reported to have 85% sensitivity in leave-one-out cross validation, and 92% in an independent set of 125 tumors representing 25 of the 30 main cancer types (4). The authors also report expanded CTID testing on 300 consecutive clinical cases. The CTID assay confirmed 78% of samples having a single suspected primary diagnosis, and resolved 74% of cases submitted with a differential diagnosis.

A retrospective, blinded, multi-site direct validation study assessed the accuracy of CTID test predictions in patients with carcinoma of unknown primary site at initial diagnosis. The tumors had latent primary sites subsequently identified during the course of clinical evaluation. Identification of latent primary sites provided a direct method, as compared to clinicopathologic correlation, to evaluate the performance of CTID in cases of unknown primary. In this study CTID testing was performed on the archived FFPE tissue of twenty-eight (28) of 38 patients whose latent primary site tumor was identified during life. Fifteen (15) of the 20 assay predictions (75% accuracy) were correct as compared to the latent primary sites identified subsequent to the original UPC diagnosis (7). Primary sites identified included breast, ovary/primary peritoneal, non-small cell lung, colorectal, gastric and melanoma. Three predictions were incorrect (intestinal, testicular, sarcoma) in patients with gastroesophageal, pancreatic, and non-small cell lung cancer, respectively. Two were unclassifiable. The study is limited by the small sample size, absent use of more contemporary IHC stains to establish the UPC diagnosis (used older archived samples and pathology reports) and confounding of “carcinoma of unknown primary site” with study set markers of mesenchymal, lymphoid and germ cell tumors, as well as CTID predictions of sarcoma and melanoma (7).

In another retrospective study, CTID identified 62 cases with squamous cell lung cancer. Twenty-nine cases (47%) were diagnosed as squamous cell carcinoma by clinicopathologic evaluation prior to submission for CTID testing. In 44% of the 29 cases, lung origin was the single suspected site or was listed in the differential diagnosis either based on morphology or supported by IHC. Data extracted from complete pathology reports showed that antibody-based classification by IHC was performed through application of CK7, CK20 and TTF-1. Squamous cell markers p63 and CK5/6 were utilized in 21% and 15% of cases respectively. The suspected primary tumor site prior to molecular profiling included: lung (41%); unknown/uncertain (27%); lung not suspected (23%) and not specified (9%) (19).

In McGee’s study, abstracted data showed that CTID testing was performed to: resolve a differential diagnosis (47%); confirm a single suspected primary site (21%); or to identify an unknown/uncertain primary tumor origin (32%). After molecular profiling, lung origin was determined for 15 of 19 cases (68%) and 2 cases were of head and neck origin. Clinical summary data obtained from treating oncologists demonstrates that CTID results guided or confirmed the primary tumor site for treatment purposes in 50% of cases (10 of 20) and changed the clinical diagnosis of the primary tumor site in an additional 35% of cases (7 of 20) (19). Small sample size and the lack of direct clinical validation limit this retrospective study.

Another retrospective study evaluated the results of site-specific treatment in a group of UPC patients in whom molecular profiling predicted a colorectal site of origin. Forty-two physicians (42 of 125 surveys) provided clinical summary information surveys. Twenty- nine patients (69%) had metastases limited to abdominal sites. Colonoscopy was negative in 32 patients. Thirty-six (36 of 42) patients had a histological diagnosis of adenocarcinoma with IHC stains (17 of 39) suggestive of colorectal origin. Thirty-two (32) patients received either first-line or second-line colorectal chemotherapy regimens. Response rates were 48% and 53% respectively. Patients who received first-line empiric therapy for UPC had an overall response rate of 21%. The median survival of patients who received site-specific therapy for colorectal cancer was 27 months compared to historical median survival of UPC patients (8-11 months) treated with empiric UPC regimens (10).

In a first-of-its-kind prospective clinical trial initiated in 2008, the clinical utility of CTID in directing therapy is being examined in patients diagnosed with UPC after standard clinical evaluation. In this trial, CTID was performed on patients with newly diagnosed UPC and treatments were based on the CTID predictions. Patients were prospectively followed with overall survival as the primary clinical endpoint. Interim results presented at ASCO 2010 demonstrated a 12.85 month median overall survival of the 61 UPC patients with sufficient follow-up (11). In comparison, median overall survival for current empiric, first-line regimens for UPC patients is estimated at 6-10 months.

Indications:

Palmetto GBA will cover TOO or CTID as a once-in-a-life time benefit. Either assay may be used to resolve an unknown primary tumor or to resolve a pathological diagnosis with 2 or more differential diagnoses.

In the unlikely event of a second UPC, denied claims can be appealed through standard Medicare protocol.

Limitations:

Use of the CTID and TOO assays are limited to:

- Tumors for which a single specific site of origin has not been established or resolved by the combination of clinicopathologic studies and consultation with pathologists, radiologists and oncologists.
- Specimens, such as cytology cell blocks, where limited quantity of the specimen precludes standard pathologic workups

Confirmatory testing of a definitive pathological diagnosis or to quality control a pathologic diagnosis is not reasonable and necessary and therefore not a covered Medicare benefit.

All other molecular profiling assays for determination of tissue origin are not reasonable and necessary and therefore not a covered Medicare benefit.

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Coding Information

Bill Type Codes:
Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

999x	Not Applicable

Revenue Codes:
Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory; unless specified in the policy services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

CPT/HCPCS Codes
GroupName
CPT Code

84999	UNLISTED CHEMISTRY PROCEDURE

ICD-9 Codes that Support Medical Necessity
Use of these codes does not guarantee reimbursement. The patient's medical record must document that the coverage criteria in this policy have been met.

196.0 - 196.9	SECONDARY AND UNSPECIFIED MALIGNANT NEOPLASM OF LYMPH NODES OF HEAD FACE AND NECK - SECONDARY AND UNSPECIFIED MALIGNANT NEOPLASM OF LYMPH NODES SITE UNSPECIFIED
199.0	DISSEMINATED MALIGNANT NEOPLASM
199.1	OTHER MALIGNANT NEOPLASM OF UNSPECIFIED SITE
239.0	NEOPLASM OF UNSPECIFIED NATURE OF DIGESTIVE SYSTEM
239.1	NEOPLASM OF UNSPECIFIED NATURE OF RESPIRATORY SYSTEM
239.2	NEOPLASM OF UNSPECIFIED NATURE OF BONE SOFT TISSUE AND SKIN
239.3	NEOPLASM OF UNSPECIFIED NATURE OF BREAST
239.4	NEOPLASM OF UNSPECIFIED NATURE OF BLADDER
239.5	NEOPLASM OF UNSPECIFIED NATURE OF OTHER GENITOURINARY ORGANS
239.6	NEOPLASM OF UNSPECIFIED NATURE OF BRAIN
239.7	NEOPLASM OF UNSPECIFIED NATURE OF ENDOCRINE GLANDS AND OTHER PARTS OF NERVOUS SYSTEM
239.89	NEOPLASMS OF UNSPECIFIED NATURE, OTHER SPECIFIED SITES
239.9	NEOPLASM OF UNSPECIFIED NATURE SITE UNSPECIFIED

Diagnoses that Support Medical Necessity
NA
ICD-9 Codes that DO NOT Support Medical Necessity
All other ICD-9 codes not listed under "ICD-9 Codes that Support Medical Necessity" will be denied as not medically necessary.

ICD-9 Codes that DO NOT Support Medical Necessity Asterisk Explanation

Diagnoses that DO NOT Support Medical Necessity
NA
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General Information

Documentations Requirements
Medical record documentation must be legible, must be maintained in the patient's medical record (hard copy or electronic copy), and must meet the criteria contained in this LCD.

For purposes of post-pay medical review bioTheranostics and Pathworks must provide this contractor with the following information and must be available to Medicare upon request:

- clinical findings, including history of prior malignant neoplasm,
- site of metastatic lesion,
- blood and imaging studies,
- surgical pathology report(s), with results of IHC marker studies and

- evidence of pathology/oncology/radiology consultation(s)

  When requesting a written redetermination (appeal) providers must include all relevant documentation with the redetermination requesgt.

Appendices

Utilization Guidelines Although the nature and extent of initial diagnostic tests are not universally defined and agreed upon, the evidence to support the use of gene-expression molecular profiling for initial provisional diagnosis of unknown primary cancer is lacking. The current standard of practice for determining a provisional diagnosis of unknown primary cancer is biopsy and standard histological examination, with immunohistochemistry where necessary. A definitive diagnosis of unknown primary cancer is established with a thorough diagnostic workup including history and physical examination, appropriate blood and imaging studies, pathologic examination and diagnosis, and consultation with pathologists, radiologists and oncologist. Gene-expression based molecular profiling is only covered after a definitive diagnosis of unknown primary cancer is established (29).

Gene-expression-based molecular profiling for unknown primary tumor should be performed only when the results will affect the treatment decision, the patient understands the potential benefits and risks of the investigation and treatment, and the patient is prepared to accept treatment.

Only one molecular profile assay for UPC (either bioTheranostic's CancerTYPE ID or Pathwork's Tissue of Origin) will be covered per patient per lifetime. All other molecular profile assays for identification of unknown primary tumors are not reasonable and necessary, and thus are not covered by Medicare.

Post-pay review will be performed to assess compliance with these utilization guidelines.

Sources of Information and Basis for Decision

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Advisory Committee Meeting Notes This policy does not reflect the sole opinion of the contractor or Contractor Medical Director. Although the final decision rests with the contractor, this policy was developed in cooperation with advisory groups, which include representatives from the affected provider community.

Contractor Advisory Committee meeting dates:
California - 01/19/2011
Hawaii - 01/13/2011
Nevada - 01/20/2011

Start Date of Comment Period 01/13/2011

End Date of Comment Period 03/07/2011

Start Date of Notice Period 06/09/2011

Revision History Number Revision #1 draft

Revision History Explanation Rev #1 06/09/2011
Revisions to this draft document are contained in the response to comments received. This revision becomes effective on 07/25/2011.

Reason for Change

Last Reviewed On Date

Related Documents

Article(s)
A51038 - Response to Comments for Molecular Profiling for Unknown Primary Cancers

LCD Attachments
There are no attachments for this LCD.

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All Versions

Updated on 06/03/2011 with effective dates 07/25/2011 - N/A
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