PHP_2.04.54	Molecular Genomic Profiling for Cancers of Unknown Primary		
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Section:	2.0 Medicine	**Page:**	Page 1 of 20

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. Department of Health Care Services (DHCS) Provider Manual Guideline:
- TAR and Non-Standard Benefits List: Codes 80000 thru 89999 (tar and non cd8)
- Pathology: Molecular Pathology (path molec)

Below is an excerpt of the Molecular Pathology guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Biomarker and Pharmacogenetic Testing
Medi-Cal covers medically necessary biomarker and pharmacogenomic testing, as described in the manual section Proprietary Laboratory Analyses (PLA). Medi-Cal may not cover all CPT and HCPCS codes associated with a particular biomarker or pharmacogenomic test. As such, the particular biomarker or pharmacogenomic test code may be covered with an approved Treatment Authorization Request (TAR) if medical necessity is established, as described in the TAR and Non-Benefit: Introduction to List section of the Provider Manual.

Biomarker Testing
Biomarker testing is used to diagnose, treat, manage, or monitor a Medi-Cal member's disease or condition to guide treatment decisions. As defined by Section 14132.09 of the Welfare and Institutions Code, biomarker testing is the analysis of an individual's tissue, blood or other biospecimen for the presence of a biomarker. Biomarker testing includes, but is not limited to, single-analyte tests, multiplex panel tests and whole genome sequencing. Biomarkers are a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a specific therapeutic intervention. A biomarker includes, but is not limited to, gene mutations or protein expression. Medically necessary biomarker testing is subject to utilization controls and evidence-based clinical practice guidelines.

When testing for biomarkers, all Medi-Cal providers must ensure that they are provided in a manner that limits disruptions to care. As with all Medi-Cal benefits, restricted or denied use of biomarker testing for the purpose of diagnosis, treatment or ongoing monitoring of any medical condition is subject to Medi-Cal's grievance, appeal and State Fair Hearing processes, as well as any additional processes established specifically for Medi-Cal managed care plans.

Pharmacogenomic Testing
Pharmacogenomic testing is defined as a laboratory genetic testing that includes, but is not limited to, a panel test to identify how a person's genetics may impact the efficacy, toxicity

and safety of medications. Medically necessary pharmacogenomic testing is covered subject to utilization controls and evidence-based clinical practice guidelines.

- Proprietary Laboratory Analyses (PLA) (prop lab)

Below is an excerpt of the guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Requirements for PLA code 0037U:
The service requires a TAR.
A TAR requires documentation of the following criteria:

- The member has either recurrent, relapsed, refractory, metastatic or advanced stages III or IV cancer, and
- The member either has not been previously tested using the same Next Generation Sequencing (NGS) test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician, and
- The decision for additional cancer treatment is contingent on the test results

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:

- APL 22-010 – Cancer Biomarker Testing

Below is an excerpt of the guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.

For the purposes of this APL, "Biomarker test" is defined as a diagnostic test, single or multigene, of an individual's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide treatment. Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some individuals with cancer. Biomarkers can determine the likelihood some types of cancer will spread. They can also help doctors choose the best treatment.

Medi-Cal managed care health plans (MCPs) are required to cover medically necessary biomarker testing for members with:

- Advanced or metastatic stage 3 or 4 cancer.
- Cancer progression or recurrence in the member with advanced or metastatic stage 3 or 4 cancer.

MCPs are prohibited from imposing prior authorization requirements on biomarker testing that is associated with a federal Food and Drug Administration (FDA)-approved therapy for advanced or metastatic stage 3 or 4 cancer. If the biomarker test is not associated with an FDA-approved cancer therapy for advanced or metastatic stage 3 or 4 cancer, MCPs may still require prior authorization for such testing.

Policy Statement

Any criteria that are not specifically addressed in the above APL and Provider Manuals, please refer to the criteria below.

I. Gene expression and/or comprehensive genomic profiling is considered **investigational** for **any** of the following:
   A. To evaluate the site of origin of a tumor of unknown primary
   B. To distinguish a primary from a metastatic tumor
   C. To guide treatment selection

   (Per Medi-Cal guidelines and for Medi-Cal members only: gene expression and/or comprehensive genomic profiling may be approved based on specific criteria listed in the State Guidelines section above.)

Policy Guidelines

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

Coding
See the Codes table for details.

Description

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.

Summary of Evidence
For individuals who have cancers of unknown primary who receive gene expression profiling and/or comprehensive genomic profiling, the evidence includes studies of clinical validity, and 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 (e.g., 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. Randomized controlled trials 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 one 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.

Additional Information
Not applicable.

Related Policies

- N/A

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

Regulatory Status

Cal. Health & Safety Code § 1367.665 and Insurance Code Section 10123.20
California laws that prohibit health plans and insurers from requiring prior authorization for biomarker testing for advanced or metastatic stage 3 or 4 cancer, and cancer progression or recurrence.

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09
California laws that require insurers to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed.

FDA Clearance of PathWork® Tissue of Origin Test™
In 2008, the PathWork® Tissue of Origin Test™ (Response Genetics; now Cancer Genetics, Cancer Genetics merged with StemoniX in 2020.) 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. The 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 (e.g., 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 Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview

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.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

Background

Cancers of Unknown Primary

Cancers of unknown primary, or occult primary malignancies, are tumors that have metastasized from an unknown primary source; they make up about 3% of all cancers in the United States.[1]

Most cancers of unknown primary are adenocarcinomas or undifferentiated tumors; less commonly, they may be squamous carcinomas, melanoma, soft tissue sarcoma, or neuroendocrine tumors. Osteo- and chondrosarcomas rarely produce cancers of unknown primary. The most common primary sites of cancers of unknown primary are lung and pancreas, followed by colon and stomach, then breast, ovary, prostate, and solid-organ carcinomas of the kidney, thyroid, and liver. Conventional methods used to aid in the identification of the origin of a cancer of unknown primary include a thorough history and physical examination; computed tomography scans of the chest, abdomen, and pelvis; routine laboratory studies; and targeted evaluation of specific signs and symptoms.[2]

Diagnosis and Classification

Cancers of unknown primary can be classified into 4 categories. Adenocarcinomas compose approximately 70% of cancers of unknown primary. Neuroendocrine tumors compose approximately 1%, squamous cell carcinomas 5%, and poorly differentiated cancer 20% to 25% of cancers of unknown primary.

Biopsy of a cancer of unknown primary with detailed pathology evaluation may include immunohistochemical analysis of the tumor. Immunohistochemical analysis identifies different

antigens present in different types of tumors and can usually distinguish an epithelial tumor (i.e., carcinoma) from melanoma or sarcoma. Detailed cytokeratin panels often allow further classification of carcinoma; however, tumors of different origins may show overlapping cytokeratin expression. Results of immunohistochemical analysis may provide a narrow differential of possible sources of a tumor's origin, but not necessarily a definitive answer.

Treatment Selection and Health Outcomes

Treatment is based on the histologic type and clinical features. About 20% of patients with cancer of unknown primary have features that guide treatment. However, about 80% of patients with cancer of unknown primary have a poor prognosis with a survival of 3 to 6 months despite a variety of chemotherapeutic combinations. Multiple sites of involvement are observed in about 50% of patients, commonly in the lungs, liver, bones and lymph nodes. The premise of tissue of origin testing in cancers of unknown primary is that identifying a likely primary tumor site will inform treatment selection leading to improved survival and other outcomes.

Molecular Genomic Profiling

Recent advances in molecular genomic profiling techniques, gene expression profiling (GEP) and comprehensive genomic profiling (CGP), have the potential to offer new therapy options to individuals with cancer of unknown primary (CUP).[3] GEP is the measurement of gene expression levels within a cell at a given timepoint, to create a global picture of cellular function, and has been used to identify the tissue of origin in individuals with CUP. The basis of these tests rest on the assumption that metastatic tumors will have similar genomic markers or a profile as the primary tumor and can help guide treatment management. Assays used in GEP utilize messenger RNA (mRNA)-, DNA-, or microRNA (miRNA)-based platforms, which analyze anywhere between 10 and 2000 genes simultaneously and can distinguish between 6 and 50 different cancer types. CGP refers to high throughput sequencing of the genome or select regions to determine the nucleotide sequence within DNA or RNA. More specifically, CGP refers to next-generation sequencing (NGS) approaches that utilize a single assay to sequence thousands of genes for genomic alterations that are associated with FDA-approved therapies. Assays used in CGP are NGS based platforms that are capable of sequencing millions of base pairs and can detect single-nucleotide polymorphisms, relocations, fusions, and copy number variants with impeccable precision.

Tests Reviewed in This Report

Selected gene expression profiling tests are described in Table 1.

Table 1. Gene Expression Profiling Tests for Cancers of Unknown Primary

Test	Manufacturer	Platform	Genes Assayed, n	Tumor Types Assessed, n
Tissue of Origin[a]	Cancer Genetics	Oligonucleotide microarray	2000	15
CancerTYPE ID	Biotheranostics	RT-qPCR	92	54

Adapted from Agwa et al (2013).[3]

RT-qPCR: real-time quantitative polymerase chain reaction.

[a] Formerly PathWork and ResponseDX: Tissue of Origin.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical

reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Gene Expression Profiling Tests for Cancers of Unknown Primary

Clinical Context and Test Purpose

The purpose of tissue of origin testing is to identify a likely primary tumor type and by doing so inform treatment selection that might lead to improved health outcomes.

Recent advances in the understanding of gene expression in normal and malignant cells have led researchers to explore molecular classification to improve the identification of the site of origin of a cancer of unknown primary. The molecular classification of cancers is based on the premise that, despite different degrees of loss of differentiation, tumors retain sufficient gene expression "signatures" as to their cell of origin, even after metastasis. Theoretically, it is possible to build a gene expression database spanning many different tumor types to compare to the expression profile of very poorly differentiated tumors or a cancer of unknown primary to aid in the identification of the tumor type and organ of origin. The feasibility of using molecular classification schemes with gene expression profiling to classify these tumors of uncertain origin has been demonstrated in several studies.[5,6,7,8]

Populations

The target populations are individuals with a cancer of unknown primary and no identified primary tumor following a standard evaluation (e.g., history, physical, imaging, pathology).

Interventions

The Tissue of Origin test (formerly known as the PathWork Tissue of Origin Test and ResponseDX: Tissue of Origin; Vyant Bio, Inc) measures the expression of 2000 genes and compares the similarity of the gene expression profiling of a cancer of unknown primary with a database of known profiles from 15 tissues with more than 60 histologic morphologies. The report generated for each tumor comprises a "similarity score," which is a measure of similarity of gene expression profiling of the specimen to the profile of the 15 known tumors in the database. Scores range from 0 (very low similarity) to 100 (very high similarity), and sum to 100 across all 15 tissues on the panel. If a single similarity score is 30 or more, it indicates that this is likely the tissue of origin. If every similarity score is between 5 and 30, the test result is considered indeterminate, and a similarity score of less than 5 rules out that tissue type as the likely origin.

An alternative method to measure gene expression is real-time quantitative polymerase chain reaction. Real-time quantitative polymerase chain reaction can be used at the practice level; however, it can only measure, at most, a few hundred genes, limiting tumor categorization to 7 or fewer types. Tumor classification accuracy rates using real-time polymerase chain reaction have been reported to be as high as 87%, but lower (71%) the more undifferentiated the tumor tested.[5] One assay that uses real-time quantitative polymerase chain reaction is the CancerTYPE ID (Biotheranostics) assay, which measures the expression of messenger RNA in a CUP tissue sample. Samples for this are formalin-fixed, paraffin-embedded tissue sections or unstained 10 mm sections on glass slides. Expression levels of 92 genes (87 tumor-associated genes and 5 reference genes for normalization) are used to detect 27 tumor types in a known database of 578 tumors with a range of 5 to 49 tumors per type. The report generated is the probability for the main cancer type, possible subtypes, tumor types not able to be excluded, and those ruled out with 95% confidence calculated by K nearest neighbor analysis. CancerTYPE ID is available with reflex to NeoTYPE Cancer Profile (NeoGenomics).

Comparators

Standard of care management is based on tumor type and probable site of origin (i.e., usual care without gene expression profiling). Because the site of origin is unknown in cancer of unknown primary, patients are typically treated with empiric chemotherapy.

Outcomes

Although test validity is relevant as a premise of the test, the outcomes informative of potential benefit include overall survival, disease-specific survival, progression-free survival, and quality of life. The premise of tissue of origin testing in cancers of unknown primary is that identifying a likely primary tumor site will inform treatment selection, leading to improved survival.

Given the generally poor survival experience of patients with cancer of unknown primary, outcomes assessed over a follow-up of 1 to 2 years are relevant.

Study Selection Criteria

For the evaluation of clinical validity of these tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Specifically, for these tests, clinical validity is the ability of a test to determine the site of origin. Demonstrating clinical validity is complicated by the lack of reference standard. Imperfect reference standards must be relied on such as the available presumptive or a reference pathologic diagnosis, known tumor types, comparisons immunohistochemistry or primary tumor diagnosed during follow-up.

Tissue of Origin Test

Five included studies reported evidence that the Tissue of Origin Test can predict a likely site of origin using a variety of reference standards: reference or available diagnosis, a primary tumor identified during follow-up, and immunohistochemical. Concordance rates in the range of 85% to 90% were reported compared with the reference standards employed.

The clinical validation study for the PathWork Tissue of Origin Test submitted to the U.S. Food and Drug Administration (FDA) in 2008 compared gene expression profiling tests for 25 to 69 samples with each of the 15 known tumors on the PathWork panel (mean, 36 specimens per known tumor). Specimens included poorly differentiated, undifferentiated, and metastatic tumors.[9] A similarity score was assigned to 545 specimens and then compared with the available specimen diagnosis. Based on the 545 results, the probability that a true tissue of origin call was obtained when a similarity score of 30 or more was reported was 93% (95% confidence interval [CI], 90% to 95%), and the probability that a true-negative tissue call was made when a similarity score of 5 or less was reported was 100% (95% CI, 100% to 100%). Overall PathWork performance comparing the profiles of the 545 specimens with the panel of 15 known tumor types showed a positive percent agreement of 90% (95% CI, 87% to 92%), negative percent agreement of 100% (95% CI, 99% to 100%), nonagreement of 6% (95% CI, 4% to 9%), and indeterminate of 4% (95% CI, 3% to 7%).

The clinical validation study for the PathWork Tissue of Origin Test Kit formalin-fixed, paraffin-embedded submitted to the FDA in 2009 compared gene expression profiling results for 25 to 57 samples with each of the 15 known tumors on the PathWork panel (mean, 31 specimens per known tumor).[9] Specimens included poorly differentiated, undifferentiated, and metastatic tumors. A similarity score was assigned to 462 specimens and then compared with the available specimen diagnosis. Based on the 462 results, the probability that a true tissue of origin call was obtained when a similarity score was reported (positive percent agreement) was 89% (95% CI, 85% to 91%), and the probability that a true negative (i.e., unknown) tissue call was made when a similarity score of 5 or

less was reported (negative percent agreement) was 99% (95% CI, 98% to 100%). The proportion of nonagreement (false-negatives) was 12% (95% CI, 9% to 15%). Further details of these data are available in the FDA's decision summary.

Monzon et al (2009) conducted a multicenter, blinded validation study of the PathWork test.[10] Specimens included poorly differentiated, undifferentiated, and metastatic tumors. A total of 351 frozen specimens and electronic files of microarray data on 271 specimens were obtained, with 547 meeting all inclusion criteria. A similarity score was given to the specimens, which was then compared with the original pathology report that accompanied the specimen. The PathWork performance comparing the profiles of the 547 specimens with the panel of 15 known tumor types showed overall sensitivity (positive percent agreement with reference diagnosis) of 88% (95% CI, 85% to 90%) and overall specificity (negative percent agreement with reference diagnosis) of 99% (95% CI, 98% to 100%), with the original pathology report acting as the reference standard. The authors noted that because there was no independent confirmation of the original pathology, using the pathology reports as the reference standard could introduce error into study results. Agreement differed by cancer type: 94% for breast and 72% for both gastric and pancreatic; these differences were statistically significant (p=.04). Agreement between the test result and reference diagnosis varied by the testing center: 88%, 84%, 92%, and 90% for Clinical Genomics facility, Cogenics, Mayo Clinic, and the International Genomics Consortium, respectively (differences not statistically significant).

Azueta et al (2013) compared immunohistochemical in formalin-fixed, paraffin-embedded tissue with the PathWork test in archived fresh-frozen tissue in a series of 32 metastatic tumors of suspected gynecologic origin (25 metastatic to the ovary, 7 peritoneal metastases).[11] The primary site of origin was determined by clinical follow-up in 29 (83%) patients and was considered the criterion standard. All peritoneal metastases originated from the ovary, and metastases to the ovary originated from the colon (11 cases), breast (5 cases), stomach (4 cases), endometrium (1 case), and an angiosarcoma (1 case). Eligible frozen sections from these cases and 3 with cancer of unknown primary were required to contain at least 60% tumor and less than 20% necrotic tissue. PathWork concordance was 86% (25/29 diagnoses); in 2 cases, diagnoses were incorrect, and 2 cases had 2 possible diagnoses. PathWork diagnosed 2 of 3 cases of the unknown primary after clinical follow-up. Immunohistochemical concordance was 79% (23/29 diagnoses); 4 cases were indeterminate, and 2 cases had 2 possible diagnoses; diagnoses of 2 of 3 cases of the unknown primary after clinical follow-up matched the PathWork diagnoses.

Handorf et al (2013) reported on a clinical validation study of formalin-fixed, paraffin-embedded metastatic cancer specimens of known primary tumors representing the 15 tissue types on the PathWork test panel.[12] PathWork's diagnostic performance was compared with immunohistochemical in 160 tumor samples. Overall concordance with known diagnoses (i.e., accuracy) was 89% for PathWork vs 83% for immunohistochemical (p=.013). In 51 poorly immunohistochemical accuracy differentiated and undifferentiated tumors, PathWork accuracy was 94%, and was 79% (p=.016). In 106 well-differentiated and moderately differentiated tumors, PathWork and immunohistochemical performance were similar (87% and 85% accuracy, respectively; p=.52). These results are based on 157 specimens for which both PathWork and immunohistochemical testing were performed; 3 specimens from the original set of 160 were considered nonevaluable by PathWork (similarity score, <20) and were excluded.

CancerTYPE ID

Results derived from 4 studies reported evidence for supporting the ability of CancerTYPE ID to predict a likely site of origin. Reference standards included a known tumor type, reference diagnosis, a primary tumor identified during follow-up, and immunohistochemical. Reported sensitivities varied according to tumor type generally ranged from 80% to over 90%.

Erlander et al (2011)[13] revised the original classifier algorithm[5] using 2,206 samples derived from multiple tumor banks and commercial sources. These samples expanded on the standard

CancerTYPE ID algorithm to increase tumor coverage and depth across 30 main cancer types and 54 histologic subtypes. Sensitivity of the classifier for the main cancer type based on internal validation (leave-one-out cross-validation) was 87% (95% CI, 85% to 88%) and, for the histologic subtype, 85% (95% CI, 83% to 86). In an independent test set of 187 samples, sensitivity was 83% (95% CI, 78% to 88%).

Kerr et al (2012) reported on a multicenter study of the 92-gene CancerTYPE ID test conducted to assess the test's clinical validity.[14] Approximately half of formalin-fixed, paraffin-embedded specimens for this study were from metastatic tumors of any grade, and the remainder from poorly differentiated primary tumors processed within 6 years of testing. Laboratory personnel at 3 study sites, blinded to all information except biopsy site and patient sex, performed diagnostic adjudication on 790 tumors, across 28 tumor types. Each specimen was then classified by class or main type and subtype with the 92-gene assay. A similarity score of 85% or greater was specified a priori as a threshold for classification, with cases falling below this value determined to be unclassifiable by the test. When results of the 92-gene test were compared with adjudicated diagnoses, the overall sensitivity of the 92-gene assay was 87% (95% CI, 84% to 89%) with a range of 48% to 100% within tumor types. The reference diagnosis was incorrectly ruled out in 5% of cases, and 6% remained unclassifiable. Test specificity was uniformly high in all tumor types, ranging from 98% to 100%. Positive predictive values ranged from 61% to 100% and exceeded 90% in 16 of 28 tumor types. In an analysis of covariance, assay performance was found to be unaffected by tissue type (i.e., metastatic or primary), histologic grade, or specimen type. A 2014 subgroup study of this dataset evaluated primary (41%) and metastatic (59%) tumors considered to have neuroendocrine differentiation (Merkel cell carcinoma, medullary thyroid carcinoma, pheochromocytoma, paraganglioma, pulmonary neuroendocrine carcinoma, pancreatic neuroendocrine carcinoma, gastrointestinal neuroendocrine carcinoma).[15] For 75 included tumors, assay sensitivities were 99% (95% CI, 93% to 99%) for classification of neuroendocrine tumor type (e.g., neuroendocrine, germ cell) and 95% (95% CI, 87% to 98%) for subtype (site of origin). Positive predictive values ranged from 83% to 100% for individual subtypes. A report by Brachtel et al (2016)[16] examined a subset of 109 patients with limited tissue studied by Kerr et al (2012) and 644 other consecutive cytology samples. In the 109 patients, sensitivity for tumor classification was 91% (95% CI, 84% to 95%), consistent with the larger sample. From the 644 cases, a sensitivity of 87% (95% CI, 84% to 89%) was estimated.

Greco et al (2013) published a retrospective, single-center study of 171 patients diagnosed with cancer of unknown primary after a clinical diagnostic workup (i.e., before immunohistochemical).[17] The study evaluated the accuracy of gene expression profiling (CancerTYPE ID) by verifying results with latent primary tumor sites found months after initial presentation (24 patients) or with immune-histochemical and/or clinicopathologic findings (147 patients). Minimum test performance thresholds were prespecified. Tumor specimens adequate for gene expression profiling were obtained in 149 (87%) patients, and diagnoses were made in 144 (96%). Of 24 patients with latent primary tumor sites, CancerTYPE ID diagnoses were accurate in 18 (75%), and IHC diagnoses were accurate in 6 (25%). Of 52 patients with the diagnosis made by immunohistochemical testing and subsequent gene expression profiling, diagnoses matched in 40 (77%). When immunohistochemical suggested 2 or 3 possible primary sites (97 patients), CancerTYPE ID diagnosis matched 1 of the proposed diagnoses in 43 (44%). Among 35 patients with discordant immunohistochemical and CancerTYPE ID diagnoses, clinicopathologic correlates and subsequent immunohistochemical supported the CancerTYPE ID diagnoses in 26 (74%). The authors concluded that gene expression profiling "complements standard pathologic evaluation" of cancer of unknown primary.

Consistent with other clinical validity data, Greco et al (2015) retrospectively reported on the use of CancerTYPE ID on archived samples from 30 patients with cancer of unknown primary and poorly differentiated neoplasms.[18] This subset of patients with cancer of unknown primary is considered potentially treatment sensitive but comprised a small number (4%) of the 751 cancer of unknown primary patients evaluated from 2000 through 2012 at Tennessee centers. A primary site was identified in 2 patients. A diagnosis was assigned by gene expression profiling in 25 (83%) of the

samples. Although 7 recently evaluated patients received treatment based on the diagnosis provided, and 5 reportedly had "favorable" outcomes, whether the benefit was obtained cannot be assessed.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs). Two published RCTs and 1 conference presentation have been identified and are summarized in Tables 2 and 3.

Hayashi et al (2019) randomized 130 patients with cancer of unknown primary to gene expression profiling directed therapy based on the predicted tissue of origin or to empirically-directed chemotherapy with paclitaxel and carboplatin.[19] A total of 101 patients received the assigned treatment and were included in the analysis. There was no significant difference between the 2 groups in the 1-year survival rate, overall survival, or progression-free survival. For example, the 1-year survival rate was 44.0% for patients who received gene expression profiling directed treatment and 54.9% for patients who received empirical chemotherapy (p=.264). The identification of more-responsive and less-responsive tissue types was prognostic for overall survival (16.7 vs 10.6 months; p=.116) and progression-free survival (5.5 vs 3.9 months; p=.018). There were several limitations to this trial which included the high percentage of patients who did not receive the assigned treatment. A major limitation in interpretation of these results is that during the trial period there were few treatments that were site specific, so there was minimal difference in the actual treatments given to the 2 groups.

The second is the Randomised Phase III Trial Comparing a Strategy Based on Molecular Analysis to the Empiric Strategy in Patients With Carcinoma of an Unknown Primary (CUP) (GEFCAPI 04) study that was presented at the 2019 Congress of the European Society for Medical Oncology in Barcelona.[20] The majority of patients in the experimental group were assessed with Cancer TYPE ID. For the entire group of experimental and control patients analyzed (N=223), there was no significant difference in overall survival (hazard ratio [HR]: 0.92; p=.71) or progression-free survival (HR: 0.95; p<.71) between patients who received site-directed therapy or empirically directed therapy of cisplatin and gemcitabine. There were 60 patients who had a gene expression profiling test with a predicted site of origin that was likely to be insensitive to cisplatin and gemcitabine, among whom overall survival for the site-directed and control groups was also not significantly different (HR: 0.74; p=.33). However, the study was underpowered for this subgroup analysis. Median overall survival in the subgroup was not improved by gene expression profiling testing (9.1 months; 95% CI, 5.65 to 14.62) compared to the control group (10.87 months; 95% CI, 3.45 to 11.73). As in the study by Hayashi et al, using a molecular test followed by tailored systemic treatment did not improve outcomes in the total population of patients with CUP.

In the CUPISCO phase 2 study, Krämer et al (2024) randomized 573 patients with unfavorable cancers of unknown primary to molecularly guided therapy (MGT) using comprehensive genomic profiling (CGP) via FoundationOne CDx or FoundationOne Liquid CDx or to platinum-based chemotherapy to evaluate the endpoint of investigator-assessed progression-free survival (PFS).[21] Individuals who received MGT or atezolizumab plus chemotherapy (intervention cohort) had a better median PFS than patients who received platinum-based chemotherapy (control cohort), however, there was no statistically significant difference in OS for patients that received either therapy regimen. A subgroup of patients that received targeted therapy with an actionable genomic alteration had longer median PFS (mPFS; 8.1 months) as compared to patients who received platinum-based chemotherapy

(mPFS=4.7 months; HR=0.65; 95% CI, 0.42 to 0.99). Furthermore, patients who were in the MGT cohort had similar or lower adverse event rates compared to the platinum-based chemotherapy cohort except for serious adverse events that lead to withdrawal of treatment and adverse events with fatal outcomes. Notable limitations of this study include the open-label design and investigator assessment of PFS. Additionally, the MGT cohort included patients who did not receive targeted therapies, due to no actionable genomic alterations but instead received atezolizumab plus chemotherapy - for which the study was not powered to assess. Given the study design limitations, it is difficult to conclude whether CGP improves the net health outcome of patients with CUP.

Limitations of these trials are summarized in Tables 4 and 5.

Table 2. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Hayashi et al (2019)[19]	Japan	14	2008-2017	Patients with CUP (130 who were randomized and had sufficient tissue for analysis)	GEP-directed therapy (50 analyzed)	Empirically directed chemotherapy with PC (51 analyzed)
Fizazi et al (2019)[20]	Europe	4	2012-2019	Patients with CUP (243)	GEP-directed therapy (110 mITT) via Cancer TYPE ID	Empirically directed chemotherapy with CG (113 mITT)
Krämer et al (2024)[21]	34 countries outside the U.S.	159	2018-2022	Patients with CUP (573)	CGP-directed therapy (436 ITT) via FoundationOne CDx or FoundationOne Liquid CDx	Empirically directed chemotherapy with CG, PC, or carboplatin and gemcitabine (110) analyzed)

CDx: companion diagnostic; CG: cisplatin and gemcitabine; CGP: comprehensive genomic profiling; CUP: cancer of unknown primary; GEP: gene expression profiling; mITT: modified intent to treat; PC: paclitaxel and carboplatin; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Results

Study	1-yr Survival Rate	Overall Survival (95% CI) mo	Progression Free Survival (95% CI) mo
Hayashi et al (2019)[19]			
N	101	101	101
GEP-directed therapy	44.0%	9.8 (5.7 to 13.8)	5.1 (1.9 to 8.3)
Empirical-PC	54.9%	12.5 (8.9 to 16.1)	4.8 (3.3 to 6.5)
HR (95% CI)		1.028 (0.678 to 1.560)	0.884 (0.590 to 1.326)
p-Value	.264	.896	.550
Fizazi et al (2019)[20]			
N		223	223
HR (95% CI)		0.92 (0.69 to 1.23)	0.95 (0.72 to 1.25)
p-Value		.71	.71
Krämer et al (2024)[21]			
N		573	573
CGP-directed therapy		14.7 (13.3 to 17.3)	6.1 (4.7 to 6.5)
Empirical chemotherapy		11.0 (9.7 to 15.4)	4.4 (4.1 to 5.6)
HR (95% CI)		0.82 (0.62 to 1.09)	0.72 (0.56 to 0.92)
p-Value		.18	.0079

CI: confidence interval; GEP: gene expression profiling; HR: hazard ratio; PC: paclitaxel and carboplatin; RCT: randomized controlled trial.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Hayashi et al (2019)[19]		4. There were few treatments available at			

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
		the time of the study that were site specific, resulting in little difference between the site specific and empiric chemotherapy treatments			
Krämer et al (2024)[21]	2. Patients with no targetable genomic alterations in the molecularly guided therapy cohort received atezolizumab plus chemotherapy				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Hayashi et al (2019)[19]	4. Following randomization, if the assay was completed but the results could not predict a tissue of origin, patients were transferred to the empiric treatment arm	1, 2, 3. No blinding		1. There was high loss to follow-up with 29 patients who did not receive the assigned therapy and were not included in the analysis	2. There was insufficient power due to the high loss to follow-up	
Krämer et al (2024)[21]					2.The trial was not powered to assess the benefit of adding atezolizumab to chemotherapy	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based

on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Tissue of Origin Test

Nystrom et al (2012) enrolled 65 physicians (from 316 approached) caring for 107 patients with cancer of unknown primary in 2009 to participate in a study of management changes following a tissue of origin test.[22] Prior to the test, physicians had no suspected diagnosis for 54 (41%) patients, which declined to 17 (16%) after testing. Changes in management were reported in 70 (65%) patients. Physicians reported test results were helpful with regard to diagnosis, choosing therapy, and triaging. Median survival was 14 months, which the authors suggested was longer than 9 months for unselected chemotherapy treated cancer of unknown primary patients. However, the low physician participation rate and lack of a concurrent comparator group limit any implications of these results. The study was supported by PathWork Diagnostics and 2 authors were company employees.

Yoon et al (2016) reported on results of a multicenter phase 2 trial evaluating combined use of carboplatin, paclitaxel, and everolimus in patients with cancer of unknown primary[23] The primary outcome was an objective response, and the study's 2-stage design with 11 or more responses in 50 assessable patients at the second stage considered success. There were 16 partial responses (objective response rate, 36%; 95% CI, 22% to 51%). Results from the PathWork Tissue of Origin Test were used post hoc to examine any association with response to therapy. In 38 of 46 patients, the test was successfully obtained, and 10 different tissues of origin were predicted. In 19 patients with a tissue of origin where platinum/taxane therapy might be considered standard therapy, objective response rates were higher compared with other patients (53% vs 26%, p=.097), accompanied by longer progression-free survival (6.4 months vs 3.5 months, p=.026; HR, 0.47; 95% CI, 0.24 to 0.93), and longer overall survival (median, 17.8 months vs 8.3 months; p=.005; HR, 0.37; 95% CI, 0.18 to 0.76). The results suggested the Tissue of Origin Test might identify platinum/taxane-sensitive tumors. However, the trial was not designed to evaluate the predictive use of the test, the Tissue of Origin data was missing for 17% of patients, and severe adverse events were common.

CancerTYPE ID

From patients with cancer of unknown primary evaluated with a CancerTYPE ID assay between 2008 and 2009, Hainsworth et al (2012) identified those with a probable (≥80%) colorectal site of origin.[24] A total of 125 patients (of 1544 results) were predicted to have primary colorectal cancer. Physicians caring for patients were sent questionnaires with a request for deidentified pathology reports 42 (34%) responded (physicians were paid $250). The date of questionnaire mailing was not reported. A total of 32 patients were given colorectal cancer regimens (16 first-line therapy only, 8 first- and second-line therapy, 8 second-line therapy only) with a reported response rate of 50% following first-line and 50% following second-line therapy; 18 patients were given empirical cancer of unknown primary regimens with a response rate of 17%. For first-line therapies, physician-assessed progression-free survival was longer following colorectal cancer regimens (8.5 months vs 6 months; p=.11). The authors concluded that "Molecular tumor profiling seems to improve survival by allowing specific therapy in this patient subgroup…." However, conclusions are limited by significant potential biases: low physician response rates and potential selection bias; unverified physician-reported retrospective assessment of progression, response, or death; absence of information on patient performance status to assess between-group prognostic differences; and the post hoc subgroup definition of uncertain generalizability to patients with cancer of unknown primary undergoing tissue of origin testing.

Hainsworth et al (2013) published a multisite prospective case series of the 92-gene CancerTYPE ID assay.[25] Formalin-fixed, paraffin-embedded biopsy specimens for this study included adenocarcinoma, poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or squamous carcinoma. A total of 289 patients were enrolled, and 252 (87%) had adequate biopsy

tissue for the assay. The molecular profiling assay predicted a tissue of origin in 247 (98%) of 252 patients. One hundred nineteen (48%) assay predictions were made with a similarity score of 80% or greater, and the rest were below 80% probability. Twenty-nine (12%) patients did not remain in the study due to decreasing performance status, brain metastases, or patient and physician decision. Of the remaining 223 patients, 194 (87%) received assay-directed chemotherapy, and 29 (13%) received standard empiric therapy. Median overall survival of the 194 patients who received assay-directed chemotherapy (67% of the original patient sample) was 12.5 months, which exceeded a prespecified improvement threshold of 30% compared with historical trial data for 396 performance-matched cancer of unknown primary patients who received standard empirical therapy at the same center. Although these results are consistent with possible benefit from gene expression profiling testing in cancer of unknown primary, potential biases accompany the nonrandomized design-confounding variables, use of subsequent lines of empirical therapy, heterogeneity of unknown primary cancers, comparison with historical controls-and limit conclusions that can be drawn.[9,26]

Section Summary: Gene Expression Profiling Tests for Cancers of Unknown Primary

To evaluate whether treatment selection can be improved, the ability of a test to suggest a likely site of origin (clinical validity) would typically be the first step in evaluation. Using different reference standards, these tests have reported sensitivities or concordances generally high (e.g., 80% to 90% or more). However, demonstrating clinical validity may be problematic because patients with cancers of unknown primary have no identified primary tumor for a reference standard. Imperfect reference standards must be relied on such as the available presumptive or a reference pathologic diagnosis, known tumor types, or comparisons immunohistochemical comparisons. A primary tumor diagnosed during follow-up might also be used as a reference standard, but its use would be subject to potential selection bias. Therefore, even substantial evidence supporting the ability of a test to suggest a likely site of origin will be insufficient to infer benefit. Convincing evidence for benefit requires demonstrating that using a test to select treatment will improve outcomes.

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 cancer of unknown primary to receive treatment based on gene expression profiling results or usual care. Two published RCTs and 1 conference presentation with this design were identified. These trials did not find a survival benefit for patients with cancer 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 one 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 CUP may have clinical utility. The absence of convincing evidence from RCTs prevents conclusions about clinical utility.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 U.S. professional society, an international society with U.S. 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. 2.2025) address the use of molecular methods to classify tumors.[3] 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 commissioned 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]

Ongoing and Unpublished Clinical Trials

A currently unpublished trial that might influence this review is listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT01540058	A Randomised Phase III Trial Comparing a Strategy Based on Molecular Analysis to the Empiric Strategy in Patients With Carcinoma of an Unknown Primary (CUP)	243	Aug 2019 (Conference Presentation)

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Family history, if applicable
  - Reason for procedure/test, when applicable
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results
  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)
- Radiology report(s) and interpretation (i.e., MRI, CT, PET)

- Other pertinent multidisciplinary notes/reports: (i.e., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management), when applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden ***(Includes FoundationOne CDx™ (F1CDx), Foundation Medicine, Inc)***
	0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations ***(Includes FoundationOne® Liquid CDx, Foundation Medicine, Inc)***
	81479	Unlisted molecular pathology procedure
	81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
	81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/01/2026	New policy.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section

51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status

In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is "experimental or investigational" by the Plan, the Plan shall refer to evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).
4. Professionals, specialists, and experts.
5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

Feedback

Blue Shield of California Promise Health Plan is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.