

## Corporate Medical Policy

### Molecular Profiling for Cancers of Unknown Primary Origin AHS-M2065

**File Name:** molecular\_profiling\_for\_cancers\_of\_unknown\_primary\_origin  
**Origination:** 1/2019  
**Last CAP Review:** 8/2020  
**Next CAP Review:** 8/2021  
**Last Review:** 8/2020

#### Description of Procedure or Service

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Cancers of unknown primary origin (CUPs) are defined as the 4-5 percent of invasive cancers for which no primary site can be identified despite an extensive diagnostic work-up (Fizazi et al., 2015; Varadhachary & Raber, 2014). CUPs are generally considered to represent metastases, and are associated with a very poor prognosis (Vikeså et al., 2015).

Gene expression assays measure the amount of specific mRNAs being transcribed to assess the genes that are active in a particular cell or tissue. Analyses of gene expression can be clinically useful for disease classification, diagnosis, prognosis, and tailoring treatment to underlying genetic determinants of pharmacologic response (Spira, 2017).

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

#### Policy

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**Molecular profiling for cancers of unknown primary origin is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.**

#### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

#### When Molecular Profiling for Cancers of Unknown Primary Origin is covered

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Not applicable

#### When Molecular Profiling for Cancers of Unknown Primary Origin is not covered

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Molecular cancer classifier and/or gene expression profiling assays is investigational to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor, or to guide site-specific therapy.

Mutational testing with next generation sequencing is considered investigational to determine targeted treatments for patients diagnosed with cancer of unknown primary origin.

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## Policy Guidelines

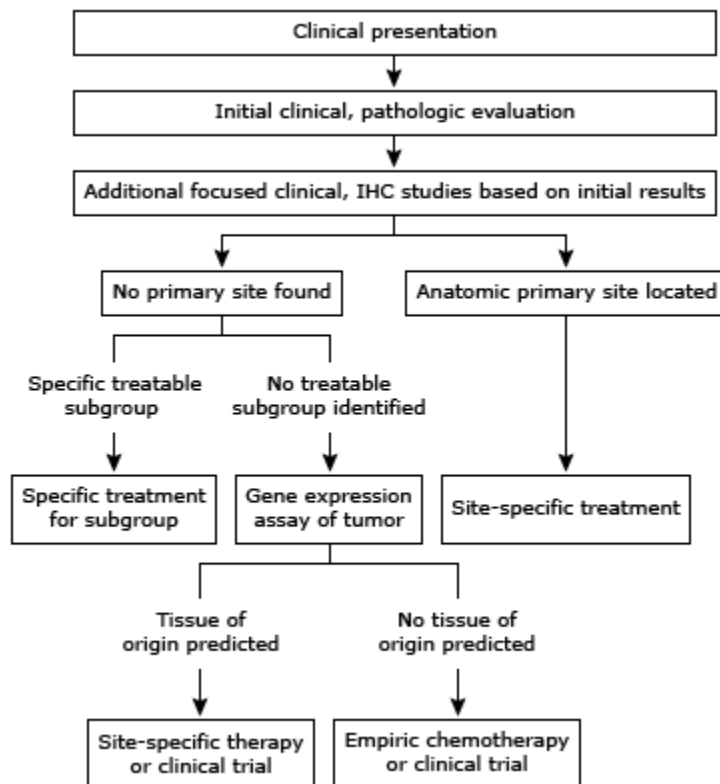
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Cancers of unknown primary origin (CUPs) typically present with symptoms attributable to metastases where subsequent work-up fails to identify the primary site (J. Hainsworth & Greco, 2017). Given their rapid progression and dissemination, it was assumed that regardless of the site of origin, the tumors in unknown primary cancers shared biologic properties common to their pathogenesis and that identification of the exact tissue of origin would not have a substantial effect on therapeutic approaches or survival (Varadhachary & Raber, 2014).

However, biologic events that allow development of metastases without a discernable tumor at the primary site have not yet been determined (Varadhachary & Raber, 2014).

Accurate prediction of the tissue of origin using immunohistochemical staining and/or gene expression profiling is now possible in most CUP cases. Appropriate classification, based upon all available evidence, is essential to identify patients for whom a specific treatment may be particularly useful and site-specific therapy based on these predictions is replacing empiric chemotherapy as the new treatment standard (J. Hainsworth & Greco, 2017). Tumors in unknown primary cancer despite different degrees of loss of differentiation retain the signature of their primary origin, even after metastasis (Fizazi et al., 2015).

Presently, patients are initially placed into one of four categories (adenocarcinoma, squamous cell carcinoma, neuroendocrine carcinoma, poorly differentiated) based upon the light microscopic examination of the initial biopsy. This classification is then used to guide further evaluation:



(F. Greco & Hainsworth, 2011)

Clinical Validity and Utility

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A number of studies have investigated the validity and diagnostic utility of gene expression profiling in addition to or in place of standard immunohistochemistry in the diagnosis and management of CUP.

Hainsworth et al (J. D. Hainsworth et al., 2013), conducted a prospective trial testing the tumor biopsy specimens from previously untreated patients with CUP with a 92-gene reverse transcriptase polymerase chain reaction cancer classification assay. Molecular tumor profiling correctly identified tissue of origin in 85% of carcinomas of known primary origin. The study showed that molecular tumor profiling predicted a tissue of origin in 247 of 252 (98%) patients with CUP. The authors concluded that “molecular tumor profiling contributes to the management of patients with CUP and should be a part of their standard evaluation.”

Greco et al (F. A. Greco, Lenington, Spigel, & Hainsworth, 2013) demonstrated that 18 of 24 patients (75%) with latent primaries discovered months to years later were predicted by molecular tumor profiling. The authors concluded that molecular tumor profiling “complements standard pathologic evaluation in determining the tissue of origin in patients with CUP, particularly when IHC is inconclusive.”

Oien and Dennis (Oien & Dennis, 2012) concluded that “in already well worked-up poorly differentiated and/or metastatic tumours, including CUP, molecular profiling performs well, with sensitivities of 72%–95% and may outperform optimal IHC by 10%–20%.” The authors conclude that molecular profiling could thus contribute to diagnosis of poorly differentiated and/or metastatic tumours.

Kerr et al. (Kerr et al., 2012) conducted a large multi-institution validation study to examine the performance of a 92-gene molecular cancer classifier. The assay showed overall sensitivities of 87% for tumor type and 82% for subtype. There was no decrease in comparative performance when metastatic tumors, high-grade tumors or cases with limited tissue were analyzed. The authors concluded that the assay showed strong performance for accurate molecular classification for various tumor histologies. They further state that “results support potential use of the assay as a standardized molecular adjunct to routine clinicopathologic evaluation for tumor classification and primary site diagnosis”

Handorf et al (Handorf et al., 2013) published the results of a prospectively conducted, blinded, multicenter study that compared the diagnostic accuracy of gene expression profiling (GEP) with IHC in identifying the primary site of metastatic tumors with known primaries. Overall, GEP accurately identified 89% of specimens, compared with 83% accuracy using IHC. In the subset of 33 poorly differentiated and undifferentiated carcinomas, GEP had higher accuracy (91%) compared to IHC (71%). The authors concluded that GEP “was significantly more accurate than IHC when used to identify the primary site of metastatic tumors.”

In a similar study design, Weiss et al (Weiss et al., 2013) compared the diagnostic accuracy of IHC analysis versus molecular classification using a 92-gene RT-PCR assay for determination of the primary tumor site. The authors reported 79% accuracy for gene expression profiling compared with 69% for immunohistochemistry. The authors concluded that the results “demonstrate superior accuracy with the 92-gene assay versus standard-of-care IHC analysis and strongly support the diagnostic utility of molecular classification in difficult-to-diagnose metastatic cancer.”

Ross et al (2015) conducted Comprehensive genomic profiling on 200 CUP formalin-fixed paraffin-embedded specimens (mean, 756× coverage) using the hybrid-capture-based FoundationOne assay for presence of targetable genomic alterations (GAs) in CUP and responses to targeted therapies. They concluded that “Almost all CUP samples harbored at least 1 clinically relevant GA with potential to influence and personalize therapy. The ACUP tumors were more frequently driven by GAs in the highly druggable RTK/Ras/mitogen-activated protein kinase (MAPK) signaling pathway than the non-ACUP tumors. Comprehensive genomic profiling can identify novel treatment paradigms to address the limited options and poor prognoses of patients with CUP.”

Santos et al (2017) aimed to develop and validate a gene-expression classifier to identify potential primary sites for metastatic cancers more accurately. “The gene-expression classifier correctly identified, by a cross-validation, 86.6% of the expected cancer superclasses of 4429 samples from the RefDB, with a specificity of 99.43%. Next, the performance of the algorithm for classifying the validation set of metastatic FFPE samples was 83.81%, with 99.04% specificity. The overall reproducibility of our gene-

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expression-classifier system was 97.22% of precision, with a coefficient of variation for inter-assays and intra-assays and intra-lots <4.1%”

Several studies indicate that gene expression assays have high diagnostic accuracy for predicting tissue of origin in cancers of unknown primary. However, the impact of these assays on patient management and patient survival remains uncertain and there is insufficient data to support its routine use. Further studies are needed to demonstrate that identifying the tissue of origin of unknown primary tumors leads to improvements in patient outcomes.

## Applicable Federal Regulations

In July 2008, the Pathwork® Tissue of Origin Test™ was cleared with limitations\* for marketing by FDA through the 510(k) process.

\* 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 (eg, CUP)

It is not intended to subclassify or modify the classification of tumors that can be diagnosed by current clinical and pathologic practice, nor to predict disease course, or survival or treatment efficacy, nor to distinguish primary from metastatic tumor.

Tumor types not in the Pathwork® Tissue of Origin test database may have RNA expression patterns that are similar to RNA expression patterns in tumor types in the database, leading to indeterminate results or misclassifications.

In June 2010, the Pathwork® Tissue of Origin Test Kit-FFPE was cleared for marketing by FDA through the 510(k) process. The 2010 clearance is an expanded application, which allows the test to be run on a patient’s FFPE tumor and has the same indications and limitations. In May 2012, minor modifications to the Pathwork® Tissue of Origin Test Kit-FFPE were determined to be substantially equivalent to the previously approved device by FDA through the 510(k) process.

Neither CancerType ID® nor miRview® (or Rosetta Cancer Origin™) have been submitted to FDA for approval.

## Guidelines and Recommendations

The 2018 National Comprehensive Cancer Network (NCCN, 2018) guidelines for the workup of an occult primary malignancy address the use of molecular methods in the classification of tumors. The guidelines state “Tumor sequencing and gene signature profiling for tissue of origin is not recommended for standard management at this time.” A footnote acknowledges that “there may be diagnostic benefit, though not necessarily clinical benefit. The use of gene signature profiling is a category 3 recommendation” The guidelines further recommend that “until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of these modalities on a case-by-case basis, with the best possible individualized patient outcome in mind.”

## National Institute for Health and Clinical Excellence

A 2010 clinical guideline from the National Institute for Health and Clinical Excellence (NICE), which was rechecked in 2014, recommended against the use of gene expression based profiling to identify primary tumors in patients with CUPs. The guideline also states “do not use gene-expression-based profiling when deciding which treatment to offer patients with confirmed CUP”(NICE, 2010).

## European Society of Medical Oncology

In 2015, the European Society of Medical Oncology (ESMO) stated that several gene expression profiling assays have become commercially available, but “their impact on patient outcome via administration of

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primary site specific therapy remains questionable and unproven in randomized trials” (Fizazi et al., 2015).

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcsnc.com](http://www.bcsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81479, 81504, 81540, 81599*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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### **For Policy Titled: Gene Expression Based Assays for Cancers of Unknown Primary**

Fizazi, K., Greco, F. A., Pavlidis, N., Daugaard, G., Oien, K., & Pentheroudakis, G. (2015). Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol, 26 Suppl 5*, v133-138. doi:10.1093/annonc/mdv305

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Hainsworth, J., & Greco, F. (2017). Overview of the classification and management of cancers of unknown primary site - UpToDate. In G. Canellos (Ed.), UpToDate. Waltham, MA. Retrieved from [https://www.uptodate.com/contents/overview-of-the-classification-and-management-of-cancers-of-unknown-primary-site?source=search\\_result&search=cancer%20unknown%20primary%20origin&selectedTitle=1~150](https://www.uptodate.com/contents/overview-of-the-classification-and-management-of-cancers-of-unknown-primary-site?source=search_result&search=cancer%20unknown%20primary%20origin&selectedTitle=1~150).

Hainsworth, J. D., Rubin, M. S., Spigel, D. R., Boccia, R. V., Raby, S., Quinn, R., & Greco, F. A. (2013). Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon research institute. *J Clin Oncol, 31*(2), 217-223. doi:10.1200/jco.2012.43.3755

Handorf, C. R., Kulkarni, A., Grenert, J. P., Weiss, L. M., Rogers, W. M., Kim, O. S., Henner, W. D. (2013). A multicenter study directly comparing the diagnostic accuracy of gene expression profiling and immunohistochemistry for primary site identification in metastatic tumors. *Am J Surg Pathol, 37*(7), 1067-1075. doi:10.1097/PAS.0b013e31828309c4

Kerr, S. E., Schnabel, C. A., Sullivan, P. S., Zhang, Y., Singh, V., Carey, B., Brachtel, E. F. (2012). Multisite validation study to determine performance characteristics of a 92-gene molecular cancer classifier. *Clin Cancer Res, 18*(14), 3952-3960. doi:10.1158/1078-0432.ccr-12-0920

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NICE. (2010). Metastatic malignant disease of unknown primary origin in adults: diagnosis and management | Guidance and guidelines | NICE. Retrieved from <https://www.nice.org.uk/guidance/cg104>

Oien, K. A., & Dennis, J. L. (2012). Diagnostic work-up of carcinoma of unknown primary: from immunohistochemistry to molecular profiling. In *Ann Oncol* (Vol. 23 Suppl 10, pp. x271-277). England.

Ross, J. S., Wang, K., Gay, L., Otto, G. A., White, E., Iwanik, K., Stephens, P. J. (2015). Comprehensive Genomic Profiling of Carcinoma of Unknown Primary Site: New Routes to Targeted Therapies. *JAMA Oncol*, 1(1), 40-49. doi:10.1001/jamaoncol.2014.216

Santos, M. T. D., Souza, B. F., Carcano, F. M., Vidal, R. O., Scapulatempo-Neto, C., Viana, C. R., & Carvalho, A. L. (2017). An integrated tool for determining the primary origin site of metastatic tumours. *J Clin Pathol*. doi:10.1136/jclinpath-2017-204887

Spira, A. S., Katrina. (2017). Tools for genetics and genomics: Gene expression profiling - UpToDate. In B. Raby (Ed.), UpToDate. Waltham, MA. Retrieved from [https://www.uptodate.com/contents/tools-for-genetics-and-genomics-gene-expression-profiling?source=search\\_result&search=gene%20expression%20array%20cancer&selectedTitle=2~150](https://www.uptodate.com/contents/tools-for-genetics-and-genomics-gene-expression-profiling?source=search_result&search=gene%20expression%20array%20cancer&selectedTitle=2~150).

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Vikeså, J., Møller, A. K. H., Kaczkowski, B., Borup, R., Winther, O., Henao, R., Nielsen, F. C. (2015). Cancers of unknown primary origin (CUP) are characterized by chromosomal instability (CIN) compared to metastasis of know origin. *BMC Cancer*, 15. doi:10.1186/s12885-015-1128-x

Weiss, L. M., Chu, P., Schroeder, B. E., Singh, V., Zhang, Y., Erlander, M. G., & Schnabel, C. A. (2013). Blinded comparator study of immunohistochemical analysis versus a 92-gene cancer classifier in the diagnosis of the primary site in metastatic tumors. *J Mol Diagn*, 15(2), 263-269. doi:10.1016/j.jmoldx.2012.10.001

Specialty Matched Consultant Advisory Panel 8/2019

Medical Director review 8/2019

## **For Policy Titled: Molecular Profiling for Cancers of Unknown Primary Origin**

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel 8/2020

## **Policy Implementation/Update Information**

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### **For Policy Titled: Gene Expression Based Assays for Cancers of Unknown Primary**

1/1/2019 New policy developed. Gene expression profiling is **investigational** to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)9/10/19 Specialty Matched Consultant Advisory Panel 8/21/2019. Reviewed by

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Avalon 2<sup>nd</sup> Quarter 2019 CAB. Deleted coding table in Billing/Coding section. Medical Director review 8/2019. (lpr)

## **For Policy Titled: Molecular Profiling for Cancers of Unknown Primary Origin**

7/28/20 Reviewed by Avalon 2<sup>nd</sup> Quarter 2020 CAB. Updated “When Not Covered” section to match new policy title and added indication. **Policy Title changed from: “Gene Expression Based Assays for Cancers of Unknown Primary” to: “Molecular Profiling for Cancers of Unknown Primary Origin.”** Medical Director review. (lpr)

9/8/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No changes to policy statement. (lpr)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.