Gene Expression Based Assays for Cancer of Unknown Primary

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DESCRIPTION

Cancers of unknown primary, or occult primary malignancies, are tumors that have metastasized from an unknown primary source; they 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.

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.

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 (ie, 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.

Gene Expression Profiling Tests for Cancer of Unknown Primary (CUP)

Test	Manufacturer	Platform	Genes Assayed	Tumor Types Assessed
CancerTYPE ID	bioTheranostics	RT-qPCR	92	54
RosettaGX Cancer Origin	Rosetta Genomics	RT-qPCR (microRNA)	64	49

Tissue of Origin (TOO) (*formerly known as the PathWork Tissue of Origin Test*)	Cancer Genetics	Oligonucleotide microarray	2000	15

RT-qPCR: real time quantitative polymerase chain reaction

Tissue of Origin (TOO) (Cancer Genetics Incorporated)
Tissue of Origin (TOO) (formerly known as PathWork Tissue of Origin Test and ResponseDX) is a gene expression test that relies on genomic information to help identify origin in cases that are metastatic and/or poorly differentiated. Tissue of Origin (TOO) measures the expression of 2,000 genes and compares the similarity of the GEP of a CUP 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 (SS), which is a measure of similarity of GEP of the specimen to the profile of the 15 known tumors in the data base. The 15 most common tumor types include thyroid, breast, non-small cell lung, pancreas, gastric, colorectal, liver, bladder, kidney, non-Hodgkin's lymphoma, melanoma, ovarian, sarcoma, testicular germ cell and prostate. Similarity Score (SS) 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.

CancerTYPE ID (bioTheranostics, Inc.)
CancerTYPE ID is a molecular cancer classifier test that helps to identify the tumor type and subtype for cancers of unknown primary (CUP) or cancers with indeterminate, uncertain or differential diagnoses. The test uses real-time RT-qPCR (real time quantitative polymerase chain reaction) to measure the expression of 92 genes (87 tumor associated genes and 5 reference genes for normalization) to detect 27 tumor types in a known database of 578 tumors with a range of 5 to 49 tumors per type.

The expression profile of 92 genes is obtained by extracting RNA from tumor-enriched sections of formalin-fixed paraffin embedded (FFPE) tissue and performing real-time quantitative RT-PCR using Taqman technology. This test identifies the most likely tissue origin and histological type based on the degree of similarity of the samples 92 gene expression profile to a reference database of gene expression profiles from tumors of known tissue origin and histological subtype. The report generated is the probability for the main cancer type, possible subtypes and tumor types not able to be excluded.

RosettaGX Cancer Origin (Rosetta Genomics)
Cancer of unknown primary (CUP) cases can represent a clinical dilemma, without knowing the primary origin, it can be difficult to select the optimal therapy for patients.

RosettaGX Cancer Origin is designed to help provide a diagnosis for such cases. RosettaGX Cancer Origin test uses custom designed microarray technology and can identify 49 cancer origins by measuring the expression level of 64 microRNAs (miRNAs).

The reported origin(s) are directly generated by algorithms (a binary decision tree classifier and KNN classifier) trained on data from 1300 known primary and metastatic tumors, with validated sensitivity of 85% or greater. MicroRNA extracted using organic solvents from formalin fixed paraffin embedded (FFPE) tissue microdissected (if necessary) to a tumor cell percentage of 60% or more. The relative expression of 64 microRNAs is quantified on a custom microarray, and their signals normalized to a reference set on the array and entered into an algorithm that combines a binary decision tree and a k-nearest-neighbor classifier to determine tumor origin among 49 possible validated cancer origins. The result is reported as either a single tumor origin or as two possible origins listed in alphabetical order. If the probability for origin(s) is below a predetermined value, no result will be reported.

Gene Expression Profiling Tests for Cancers of Unknown Primary
Clinical Context and Test Purpose
The purpose of gene expression profiling (GEP) i.e., 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 (i.e., as a predictive test).
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.

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

Interventions
Three gene expression profiling (GEP) tests currently available in the United States: Tissue of Origin (TOO), CancerTYPE ID, and RosettaGX Cancer Origin.

The Tissue of Origin test (formerly known as the PathWork Tissue of Origin Test and ResponseDX: Tissue of Origin; Cancer Genetics) 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.4, 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 of 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 (IHC) or primary tumor diagnosed during follow-up.

CancerTYPE ID
Results derived from 4 samples 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 IHC. Reported sensitivities varied according to tumor type generally ranged from 80% to over 90%.

(2016) A report by Brachtel et al. examined a subset of samples from 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%) or consistent with the larger sample. From the 644 cases, a sensitivity of 87% (95% CI, 84% to 89%) was estimated, identifying 23 different tumor types and allowing for additional mutational analysis in selected cases. These findings demonstrate high accuracy and analytical success rate of the 92-gene assay, supporting its utility in the molecular diagnosis of cancer for specimens with limited tissue.

(2015) Consistent with other clinical validity data, Greco et al. retrospectively reported on the use of CancerTYPE ID on archived samples from 30 patients with CUP and poorly differentiated neoplasms. This subset of patients with CUP is considered potentially treatment sensitive but comprised a small number (4%) of the 751 CUP patients evaluated from 2000 through 2012 at Tennessee centers. A primary site was identified in 2 patients. A diagnosis was assigned by GEP 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 benefit was obtained cannot be assessed.

(2013) Greco et al. published a retrospective, single-center study of 171 patients diagnosed with CUP after a clinical diagnostic workup (i.e., before IHC). The purpose of the study was to evaluate the accuracy of GEP (CancerTYPE ID) by verifying results with latent primary tumor sites found months after initial presentation (24 patients) or with IHC and/or clinicopathologic findings (147 patients). Minimum test performance

thresholds were prespecified. Tumor specimens adequate for GEP 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 diagnosis made by IHC testing and subsequent GEP, diagnoses matched in 40 (77%). When IHC suggested 2 or 3 possible primary sites (97 patients), CancerTYPE ID diagnosis matched one of the proposed diagnoses in 43 (44%). Among 35 patients with discordant IHC and CancerTYPE ID diagnoses, clinicopathologic correlates and subsequent IHC supported the CancerTYPE ID diagnoses in 26 (74%). The authors concluded that GEP "complements standard pathologic evaluation" of CUP.

(2012) Kerr et al. reported on a multicenter study of the 92-gene CancerTYPE ID test conducted to assess the test's clinical validity. Approximately half of FFPE 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 according to 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, 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 sub-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). 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.

(2011) Erlander et al. revised the original classifier algorithm3 using 2206 samples created 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%). These findings provide further support that broad and diverse tumor classification can be performed using a relatively compact gene set. An additional 300 consecutive cases

submitted for clinical testing were profiled to characterize clinical utility in a real-world setting: the 92-gene assay confirmed 78% of samples having a single suspected primary tumor and provided a single molecular prediction in 74% of cases with two or more differential diagnoses. Further development of the 92-gene RT-PCR assay has resulted in a significant expansion in reportable tumor types and histological features with strong performance characteristics and supports the use of molecular classification as an objective standardized adjunct to current methods.

RosettaGX Cancer Origin

(2012) Meiri et al. assessed the clinical validity of the miRview mets2 test in 509 FFPE specimens. Four hundred eighty-nine of these samples were successfully processed, and results were compared with the known origin of the specimen. Sensitivity of the test was 86%, and specificity exceeded 99%. Three smaller clinical validation studies testing 83 to 204 samples reported similar sensitivity and specificity, with ranges of 84% to 86% and 95% to 99%, respectively.

Tissue of Origin (TOO) Test

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 immunohistochemistry (IHC). Concordance rates in the range of 85% to 90% were reported compared with the reference standards employed.

(2013) Azueta et al. compared IHC in FFPE tissue and 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). 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 CUP 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 unknown primary after clinical follow-up. IHC concordance was 79% (23/29 diagnoses); 4 cases were indeterminate, and 2 cases had 2 possible diagnoses; diagnoses of 2 of 3 cases of unknown primary after clinical follow-up matched the PathWork diagnoses.

(2013) Handorf et al. reported on a clinical validation study of FFPE metastatic cancer specimens of known primary tumors representing the 15 tissue types on the PathWork test panel. PathWork's diagnostic performance was compared with IHC in 160 tumor samples. Overall concordance with known diagnoses (i.e., accuracy) was 89% for PathWork versus 83% for IHC (p=0.013). In 51 poorly differentiated and undifferentiated tumors, PathWork accuracy was 94% and IHC accuracy was 79% (p=0.016). In 106 well-differentiated and moderately differentiated tumors, PathWork and IHC performance was similar (87% and 85% accuracy, respectively; p=0.52). These results are based on 157 specimens for which both PathWork and IHC testing were performed; 3 specimens from

the original set of 160 were considered nonevaluable by PathWork (similarity score, <20) and were excluded.

(2009) Monzon et al. conducted a multicenter blinded validation study of the PathWork test. 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=0.04). Agreement between test result and reference diagnosis varied by testing center: 88%, 84%, 92%, and 90% for Clinical Genomics facility, Cogenics, Mayo Clinic, and the International Genomics Consortium, respectively (differences not statistically significant).

(2009) The clinical validation study for the PathWork Tissue of Origin Test Kit-FFPE submitted to FDA in 2009 compared GEP results for 25 to 57 samples to each of the 15 known tumors on the PathWork panel (mean, 31 specimens per known tumor). 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 FDA's decision summary.

(2008) The clinical validation study for the PathWork Tissue of Origin Test that was submitted to FDA in 2008 compared GEP 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. 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%).

Section Summary Clinically Valid
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 (eg, 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.

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.

CancerTYPE ID
(2019) Hayashi et al randomized 130 patients with cancer of unknown primary (CUP) to gene expression profiling directed therapy based on the predicted tissue of origin or to empirically directed chemotherapy with paclitaxel and carboplatin. A total of 101 patients received the assigned treatment and were included in the analysis. There was no significant difference between the two 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 versus 10.6 months; p =.116) and progression-free survival (5.5 versus 3.9 months; p =.018), both respectively. 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 two groups.

(2019) Fizazi et al. completed the second Randomized 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 (ESMO) in Barcelona. 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: 0.92, p=0.71) or progression-free survival (hazard ratio: 0.95, p<0.71) 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 (hazard ratio:0.74, p=0.33). 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% confidence interval: 5.65;14.62] compared to the control group 10.87 months [95% confidence interval 3.45;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 cancer of unknown primary (CUP).

Summary of Key RCT Characteristics

Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
					Active	***Comparator***
Hayashi et al (2019)	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)	Europe	4	2012-2019	Patients with CUP (243)	GEP-directed therapy (110 mITT)	Empirically directed chemotherapy with CG (113 mITT)

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

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)			
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	0.264	0.896	0.550
Fizazi et al (2019)			
N		223	223
HR (95% CI)		0.92 (0.69-1.23)	0.95 (0.72-1.25)
p-Value		.71	.71

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

Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Hayashi et al. (2019)		4. There were few treatments available at the time of the study that were site specific, resulting in little difference between the site specific and empiric chemotherapy treatments			

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.

Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Hayashi et al. (2019)	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.	

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.

(2013) Hainsworth et al. published a multisite prospective case series of the 92-gene CancerTYPE ID assay. FFPE 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 CUP patients who received standard empiric therapy at the same center. Although these results are consistent with possible benefit from GEP testing in CUP, 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.

(2012) From patients with CUP who had undergone a CancerTYPE ID assay between March 2008 and August 2009, Hainsworth et al identified those with a probable (≥80%) colorectal site of origin. A total of 125 patients (of 1544 results) were predicted to have a primary colorectal cancer (CRC). 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 CRC 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 empiric CUP regimens with a response rate of 17%. For first-line therapies, physician-assessed PFS was longer following CRC regimens—8.5 months versus 6 months (p=0.11). 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 CUP undergoing tissue of origin testing.

RosettaGX Cancer Origin

No published data on the clinical utility of RosettaGX Cancer Origin test and impact on patient treatment decision or diagnosis were identified in the literature.

Tissue of Origin (TOO) Test

(2016) Yoon et al. reported results of a multicenter phase 2 trial evaluating combined use of carboplatin, paclitaxel, and everolimus in patients with CUP. The primary outcome was objective response, and the study a 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%). Grade 3 or 4 adverse events occurred in 40 (87%) patients. 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=0.097), accompanied by longer progression-free survival (PFS; 6.4 months vs 3.5 months, p=0.026; hazard ratio [HR], 0.47; 95% CI, 0.24 to 0.93), and longer OS (median, 17.8 months vs 8.3 months; p=0.005; HR=0.37; 95% CI, 0.18 to 0.76). The results suggested a tissue of origin test might identify platinum/taxane-

sensitive tumors. However, the study was not designed to evaluate predictive use of the test, tissue of origin data was missing for 17% of patients, and severe adverse events were common.

(2012) Nystrom et al. enrolled 65 physicians (from 316 approached) caring for 107 patients with CUP in 2009 to participate in a study of management changes following a tissue of origin test. 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 suggest longer than 9 months for unselected chemotherapy treated CUP patients. However, the low physician participation rate and lack of a concurrent comparator group limits any implications of these results. The study was supported by PathWork Diagnostics and two authors company employees.

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. 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.

(2013) Hainsworth et al. published a multisite prospective case series of the 92-gene CancerTYPE ID assay. 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.

Section Summary: Clinically Useful
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. One published RCT 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 the second 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.

Summary of Evidence
For individuals who have a cancer of unknown primary (CUP) who receive gene expression profiling (GEP), the evidence includes studies of clinical validity, randomized control trials (RCTs) that have evaluated clinical utility. Of the commercially available tests reviewed, one has been cleared by the Food and Drug Administration (FDA) (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, 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 patient with cancers of unknown primary (CUP) to receive treatment based on gene expression profiling results or usual care. One published RCT and one conference presentation with this design were identified. These trials did not find a survival benefit for patients with cancers of unknown primary (CUP) 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 two groups. In the second RCT, most primary cancers were not insensitive 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. Well-designed randomized controlled trials (RCTs) are needed to determine the clinical utility of gene expression profiling to identify the tissue of origin for cancers of unknown primary site compared with traditional clinicopathologic factors to guide medical management and improve clinical outcomes. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American Cancer Society (ACS)
(2018) The American Cancer Society provided statements on, "Can a Cancer of an Unknown Primary Be Found Early" with specific information about tests that may help detect breast, prostate, cervical, and colorectal cancers early, before they cause any symptoms.

- "…these cancers account for a fairly small portion of cancers of unknown primary. No screening tests have been proven to be effective in the early detection of many of the cancers that are likely to be diagnosed as cancer of unknown primary, such as pancreatic, stomach, and kidney cancers." *(Accessed November 2022)*

(2018) The American Cancer Society has information for a Test for Cancer of an Unknown Primary specific to gene expression profiling noting the following,

- "With advances in technology, some newer lab tests are able to look at the activity of many genes in the cancer cells at the same time. By comparing the pattern of gene activity in the CUP sample to the patterns of activity seen with known types of cancer, doctors can sometimes get a better idea of where a cancer started. These tests can sometimes help your doctor discover where the cancer may have started, but so far, they haven't been linked to better outcomes in patients." (*Accessed November 2022*)

European Society of Medical Oncology
(2015) The guideline from the European Society of Medical Oncology (ESMO) cancers of unknown primary site: ESMO clinical practice guidelines for diagnosis, treatment and follow-up states that

- "several gene expression profiling assays have become commercially available claiming to blindly and correctly identify a known primary cancer and a likely tissue of origin in patients with cancer of unknown primary (CUP). These assays are based on mRNA, miRNA RT-PCR or oligonucleotide microarray technologies. No significant differences in the tumor microRNA expression profile were evident when cancer of unknown primary (CUP) metastases biologically assigned to a primary tissue origin were compared with metastases

from typical solid tumors of known origin. These tests may aid in the diagnosis of the putative primary tumor site in some patients, however, their impact on patient outcome via administration of primary site-specific therapy remains questionable and unproven in randomized trials". (IV, C)

- IV Retrospective cohort studies or case-control studies; C insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, cost, etc.) Optional *(Accessed November 2022*)

National Cancer Institute (NCI)
(2018) Gene expression profiling: Gene expression profiling using an immunohistochemical panel may allow identification of a potential site of origin in patients with adenocarcinoma of unknown origin. One study reported identification of a potential primary site in 14 of 22 patients. This modality has not been validated against the gold standard and has not been studied prospectively. (*Accessed November 2022*)

National Comprehensive Cancer Network (NCCN)
The current National Comprehensive Cancer Network (NCCN) guidelines for Occult Primary (Cancer of Unknown Primary [CUP]) version 2.2023 address molecular profiling to identify the tissue of origin in cancer unknown primary (CUP). The guideline states:

Pathology
In an attempt to identify the tissue of origin, biopsy of 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 cancer. Both methodologies offer a simar range of accuracy in tumor classification (approximately 75%). While there may be a diagnostic benefit to GEP, a clinical benefit has not been demonstrated. Consequently, the panel does not currently recommend use of gene sequencing to predict tissue of origin. Next-generation sequencing (NGS) can be considered after an initial determination of histology has been made as a way to identify potentially actionable genomic aberrations that would guide therapeutic decision-making. Until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of IHC, GEP, and NGS on a case-by-case basis with the best possible individualized patient outcome in mind.

Molecular Profiling
Recent advances in molecular profiling techniques can potentially offer new therapy options to patients with CUP; however, the clinical benefit of using molecular profiling to guide treatment decisions in CUP remains to be determined. There are two main applications for molecular profiling in the management of CUP. The first application utilizes GEP and molecular cancer classifier assays to determine the tissue of origin to guide site – specific therapy. The second application utilizes NGS to identify genomic aberrations that can be targeted therapeutically.

GEP and Molecular Cancer Classifier Assays for Tissue of Origin
Over the past decade, several studies have examined various molecular assays designed to identify the tissue of origin in CUP. These assays are designed based on the assumption that metastatic tumors will have a similar molecular profile to that of the primary tumor. 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. When compared to samples from known tumor types, these assays have generally demonstrated an accuracy rate of 85% to 90% in determining the tissue of origin. However, because it is difficult to confirm the site of origin in most cases of CUP, the accuracy of GEP assays in occult primary tumor samples is challenging to determine. Surrogate measures used to determine accuracy include correlation with IHC findings, clinical presentation/response to therapy, as well as the appearance of latent disease at the primary tumor site. Several studies suggest that the accuracy of GEP profiling is comparable or superior to the accuracy of IHC for poorly differentiated/undifferentiated carcinomas.

Several commercially available GEP tests have been evaluated in prospective clinical studies in an attempt to determine if the information they provide regarding tissue of origin translates into clinically meaningful benefits for patients. Comparison between commercially available GEP tests have also been published. Currently, there is no evidence of improved outcomes with the use of site-specific therapy guided by molecular testing results in CUP patients. Results from a prospective phase II study of 194 patients with CUP in which treatments were based on the identification of primary sites by a 92 gene assay showed that clinical features and response to treatment were generally consistent with assay results. However, while the median survival time of 12.5 months in the subset of patients who received GEP-directed treatment was better than the predefined historical cohort, the difference was small and similar results could be expected from the empiric use of these regimens in a good PS group of patients with CUP predominately below the diaphragm. In a recently published randomized phase II trial conducted in Japan, GEP-based site-specific treatment did not significantly improve 1-year survival compared with empirical carboplatin plus paclitaxel in patients with CUP. The randomized phase III GEFCAPI04 trial directly compared the clinical effectiveness of systemic treatment based on GEP results to empiric chemotherapy with cisplatin and gemcitabine in 243 European patients with CUP.57 Median progression-free survival (PFS) and OS were similar between the two groups. Although GEP-based site-specific treatment did not improve outcomes, it is important to note that many patients in this trial had cancers that are difficult to treat and for which no targeted therapies are available (ie, pancreatico-biliary cancer). Molecular testing in a small number of patients with suspected primary cancers unlikely to respond to empiric chemotherapy allowed the use of a targeted agent or better tailored therapy. However, there were not enough of these patients to impact the overall trial results. Thus, the clinical benefit that might be derived from the use of GEP assays, if any, remains to be determined.

National Institute for Health and Care Excellence (NICE)
A 2010 clinical guidance from the National Institute for Health and Care Excellence recommended against the use of gene expression profiling to identify primary tumors in patients with cancers of unknown primary.

- This recommendation was based on "limited evidence that gene-expression based profiling changes the management of patients with cancer of unknown primary and no evidence of improvement in outcome." The guidance included a research recommendation for trials to assess the clinical utility of gene expression profiling. (*Accessed November 2022*)

Regulatory Status
(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 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. The database contains examples of RNA expression patterns for 15 common malignant tumor types.

A PathWork® Tissue of Origin® Test result was intended for use in the context of the patient's clinical history and other diagnostic tests evaluated by a qualified clinician. 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.

(2010) The PathWork® Tissue of Origin Test Kit-FFPE was cleared for marketing by FDA through the 510(k) process. The 2010 clearance was an expanded application, which permitted the test to be run on a patient's formalin-fixed, paraffin-embedded (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.

The test is now offered by Cancer Genetics, as the Tissue of Origin® test.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). CancerTYPE ID® (Biotheranostics, San Diego, CA) or RosettaGX Cancer Origin™ (Rosetta Genomics, Philadelphia, PA) are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

PRIOR APPROVAL

Not applicable.

POLICY

Gene expression profiling is considered **investigational** to identify the tissue of origin for cancers of unknown primary (CUP), distinguish a primary from metastatic tumor, or to guide site-specific therapy to include but not limited to the following because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- Tissue of Origin (TOO) Test
- CancerTYPE ID
- RosettaGX Cancer Origin Test

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81504 Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported on tissue similarity score (Tissue of Origin Test)
- 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 predicted main cancer type and subtype (CancerTYPE ID)
- 81479 Unlisted molecular pathology procedure (*may be used for RosettaGX Cancer Origin test*)
- 81599 Unlisted multianalyte with algorithmic analyses (*may be used for RosettaGX Cancer Origin test*)

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- UpToDate. Adenocarcinoma of Unknown Primary Site. John D. Hainsworth M.D., F. Anthony Greco M.D., Topic last updated March 15, 2019. Also available at https://www.uptodate.com
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POLICY HISTORY		
Date	**Reason**	**Action**
December 2022	Annual Review	Policy Revised
December 2021	Annual Review	Policy Renewed
December 2020	Annual Review	Policy Revised
December 2019	Annual Review	Policy Renewed
December 2018	Annual Review	Policy Renewed
December 2017		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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