



# Geisinger Health Plan Policies and Procedure Manual

**Policy: MP262**

**Section: Medical Benefit Policy**

**Subject: Microarray-based Gene Expression Testing for Cancer of Unknown Origin**

**Applicable line of business:**

<b>Commercial</b>	<b>x</b>	<b>Medicaid</b>	<b>x</b>
<b>Medicare</b>	<b>x</b>	<b>ACA</b>	<b>x</b>
<b>CHIP</b>	<b>x</b>		

**I. Policy:** Microarray-based Gene Expression testing for Cancer of Unknown Origin

**II. Purpose/Objective:**

To provide a policy of coverage regarding Microarray-based Gene Expression testing for Cancer of Unknown Origin

**III. Responsibility:**

- A. Medical Directors
- B. Medical Management

**IV. Required Definitions**

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

**Commercial**

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

**Medicare**

Geisinger Gold Medicare Advantage HMO, PPO, and HMO D-SNP plans are offered by Geisinger Health Plan/Geisinger Indemnity Insurance Company, health plans with a Medicare contract. Continued enrollment in Geisinger Gold depends on contract renewal. Geisinger Health Plan/Geisinger Indemnity Insurance Company are part of Geisinger, an integrated health care delivery and coverage organization.

**CHIP**

Geisinger Health Plan Kids (GHP Kids) is a Children's Health Insurance Program (CHIP) offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

**Medicaid**

Geisinger Health Plan Family (GHP Family) is a Medical Assistance (Medicaid) insurance program offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

## V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

- a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
- b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
- c. in accordance with current standards of good medical treatment practiced by the general medical community.
- d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
- e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

### Medicaid Business Segment

Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age

### DESCRIPTION:

Microarray-based gene expression testing measures the expression of more than 1,500 genes, and compares the similarity of the gene expression profile of a cancer of unknown primary to a database of known profiles from 15 tissues with more than 60 histologic morphologies. The test provides a score which is a measure of similarity of the gene expression profile 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). Single similarity scores greater than or equal to 30 indicate that this is likely the tissue of origin. Similarity scores between 5 and 30 are considered indeterminate, and scores of less than 5 rule out that tissue type as the likely origin.

### LIMITATIONS:

#### For Medicare and Medicaid business segments:

Palmetto GBA, the contractor that administers Medicare in California, has issued a positive coverage policy for FDA-approved microarray-based gene expression testing (e.g., Pathwork® Tissue of Origin Test, CancerTYPE ID® Test,). The Palmetto GBA coverage policy is applicable for all Medicare patients nationally.

### MEDICARE BUSINESS SEGMENT:

Per Local Carrier Determination Biomarkers for Oncology (L34796) the Rosetta Cancer Origin Test™, CancerTYPE ID® Test is “considered reasonable and necessary in the pathologic diagnoses of cancer of unknown primary when a conventional surgical pathology/imaging work-up is unable to identify a primary neoplastic site. Other applications of this technology are non-covered and considered investigational in the use of diagnosis of specific tumor types such as NSCLC and renal cancers.”

### EXCLUSIONS:

Unless mandated coverage exists, the Plan does **NOT** provide coverage for the use of microarray-based expression testing for cancer of unknown origin, including but not limited to Pathwork® Tissue of Origin Test, Pathwork TOO Frozen Array; CancerTYPE ID® Test, Rosetta Cancer Origin test; miRview®; ProOnc TumorSourceDX™, DecisionDX-G-CIMP to evaluate the site of origin of a tumor of unknown primary, and to distinguish a primary from a metastatic tumor because it is considered experimental, investigational or unproven. There is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this test on health outcomes when compared to established tests or technologies.

### Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

**Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.**

**CODING ASSOCIATED WITH:**

*The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at [www.cms.gov](http://www.cms.gov) or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.*

81479 Unlisted molecular pathology procedure (RosettaGX Cancer Origin test)

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 (CancerTYPE ID)

81599 Unlisted multianalyte with algorithmic analyses (RosettaGX Cancer Origin test)

Current Procedural Terminology (CPT®) © American Medical Association: Chicago, IL.

**LINE OF BUSINESS:**

**Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.**

**REFERENCES:**

Dumur EI, Lyons-Weiler M, Sciulli C et al. Interlaboratory performance of a microarray-based gene expression test to determine tissue of origin in poorly differentiated and undifferentiated cancers. J Mol Diagn 2008. 10(1):67-77.

Monzon FA, Lyons-Weiler M, Buturovic LJ et al. Multicenter validation of a 1,550-gene expression profile for identification of tumor tissue of origin. J Clin Oncol.2008;27(15):2503-08.

Stancel GA, Coffey D, Alvarez K et al. Identification of tissue of origin in body fluid specimens using a gene expression microarray assay. Cancer Cytopathol. 2011 Jun 29. doi: 10.1002/cncy.20167. [Epub ahead of print].

Beck AH, Rodriguez-Paris J, Zehnder J et al. Evaluation of a gene expression microarray-based assay to determine tissue type of origin on a diverse set of 49 malignancies. Am J Surg Pathol. 2011 Jul;35(7):1030-7.

Grenert JP, Smith A, Ruan W et al. Gene expression profiling from formalin-fixed, paraffin-embedded tissue for tumor diagnosis. Clin Chim Acta. 2011 Jul 15;412(15-16):1462-4. Epub 2011 Apr 7.

Pillai R, Deeter R, Rigl CT. Validation and reproducibility of a microarray-based gene expression test for tumor identification in formalin-fixed, paraffin-embedded specimens. J Mol Diagn. 2011 Jan;13(1):48-56. Epub 2010 Dec 23.

Wu AH, Drees JC, Wang H et al. Gene expression profiles help identify the tissue of origin for metastatic brain cancers. Diagn Pathol. 2010 Apr 26;5:26.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: occult primary (cancer of unknown primary [CUP]). Version National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in OncologyTM. Occult Primary v2.2021

Horlings, HM, van Laar, RK, Kerst, JM, et al. Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinomas of unknown primary. J Clin Oncol. 2008 Sep 20;26(27):4435-41.

Ma, XJ, Patel, R, Wang, X, et al. Molecular classification of human cancers using a 92-gene real-time quantitative polymerase chain reaction assay. Arch Pathol Lab Med. 2006 Apr;130(4):465-73.

Novitas Solutions. Local Coverage Determination (LCD): Biomarkers for Oncology (L34796)  
[https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35396&ver=50&name=314\\*1&UpdatePeriod=672&bc=AQAAEAAAAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35396&ver=50&name=314*1&UpdatePeriod=672&bc=AQAAEAAAAAAAAAA%3d%3d&)

Greco FA, Lenington WJ, Spigel DR, Hainsworth JD. Poorly differentiated neoplasms of unknown primary site: diagnostic usefulness of a molecular cancer classifier assay. Mol Diagn Ther. Apr 2015; 19(2):91-97.

Prasad V, Oseran A, Fakhrehani F. The use of gene expression profiling and mutation analysis increases the cost of care for patients with carcinoma of unknown primary; does it also improve survival? Eur J Cancer. Feb 2016;54:159-162

Yoon HH, Foster NR, Meyers JP, et al. Gene expression profiling identifies responsive patients with cancer of unknown primary treated with carboplatin, paclitaxel, and everolimus: NCCTG N0871 (alliance). Ann Oncol. Feb 2016;27(2):339-344.

Hayashi H, Kurata T, Takigushi Y, et. al. Randomized phase II trial comparing site specific treatment based on gene expression profiling with carboplatin and paclitaxel for patients with cancer of unknown primary site. J Clin Oncol 2019 Mar 1;37(7):570-579

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Occult Primary. V2.2025

Sun W, Wu W, Wang Q, et al. Clinical validation of a 90-gene expression test for tumor tissue of origin diagnosis: a large-scale multicenter study of 1417 patients. J Transl Med. 2022;20(1):114. Published 2022 Mar 7. doi:10.1186/s12967-022-03318-6

This policy will be revised as necessary and reviewed no less than annually.

**Devised:** 2/12

**Revised:** 11/14 (added Medicare indication), 11/15 (added CancerTYPE ID® Test); 1/17

**Reviewed:** 2/13, 2/14, 12/17, 12/18, 12/19, 12/20, 12/21, 12/22, 12/23, 1/25

**CMS UM Oversight Committee Approval:** 12/23, 5/24, 2/25

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at <https://www.geisinger.org/health-plan/providers/ghp-clinical-policies>

Please be advised that the use of the logos, service marks or names of Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company on a marketing, press releases or any communication piece regarding the contents of this medical policy is strictly prohibited without the prior written consent of Geisinger Health Plan. Additionally, the above medical policy does not confer any endorsement by Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company regarding the medical service, medical device or medical lab test described under this medical policy.