Harvard Pilgrim Health Care | TUFTS Health Plan

Medical Necessity Guidelines:

Genetic Testing – Gene Expression for Cancer of Unknown Primary (CUP)

Effective: November 4, 2026

Prior Authorization Required If REQUIRED, submit supporting clinical documentation pertinent to service request to the FAX numbers below	Yes ☒ No ☐
Notification Required IF REQUIRED, concurrent review may apply	Yes ☐ No ☒

Applies to:

Commercial Products

☐ Harvard Pilgrim Health Care Commercial products; 800-232-0816
☒ Tufts Health Plan Commercial products; 617-972-9409

Public Plans Products

☐ Tufts Health Direct – A Massachusetts Qualified Health Plan (QHP) (a commercial product); 888-415-9055
☐ Tufts Health Together – MassHealth Accountable Care Partnership Plans; 888-415-9055
☐ Tufts Health RITogether – A Rhode Island Medicaid Plan; 857-304-6404
☐ Tufts Health One Care – A dual-eligible product; 857-304-6304

Senior Products

☐ Tufts Health Plan Senior Care Options (SCO), (a dual-eligible product); 617-972-9409
☐ Tufts Medicare Preferred HMO, (a Medicare Advantage product); 617-972-9409
☐ Tufts Medicare Preferred PPO, (a Medicare Advantage product); 617-972-9409

Note: While you may not be the provider responsible for obtaining prior authorization or notifying Point32Health, as a condition of payment you will need to ensure that any necessary prior authorization has been obtained and/or Point32Health has received proper notification. If notification is required, providers may additionally be required to provide updated clinical information to qualify for continued service.

Overview

Gene expression testing for cancers of unknown primary (CUP) is used to aid in the diagnosis and treatment of metastatic cancers for which the site of primary remains uncertain or unknown after a complete medical work-up.

Clinical Guideline Coverage Criteria

The Plan may authorize the coverage of a gene expression testing assay for CUP when the test is ordered by an oncologist and **ALL** of the following are met:

1. The Member has the diagnosis of metastatic cancer; **and**
2. Clinical evaluation has failed to identify the primary site (tissue of origin) of the cancer; **and**
3. The pathology report is submitted to The Plan for review; **and**
4. Pathology examination of the tumor is not able to conclusively identify the primary site or has identified two or more possible primary sites.

Limitations

The Plan will not cover this test when used to confirm a diagnosis.

Codes

The following code(s) require prior authorization:

Table 1: CPT/HCPCS Codes

Code	Description
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores (Pathwork® Tissue of Origin Test, Pathwork Diagnostics)
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, bioTheranostics, Inc.)

References:

1. Laouri, M, Halks-Miller, M., Henner, D. & J Scott Nystrom. Potential clinical utility of gene-expression profiling in identifying tumors of uncertain origin. Personalized Medicine (2011)8(6), 615–622.
2. CancerTYPE ID® (bioTheranostics Inc.) Hayesinc.com/login [via subscription only]. Published July 30, 2018. Updated. March 25 2022. Accessed August 19, 2025.
3. CancerTYPE ID® (bioTheranostics Inc.) Precision Medicine Research Brief. Hayesinc.com/login [via subscription only]. Published April 24 2023. Accessed August 19, 2025.
4. Berger BM, Hanna GJ, Posner MR, et al. Detection of occult recurrence using circulating tumor tissue modified viral HPV DNA among patients treated for HPV-driven oropharyngeal carcinoma. Clin Cancer Res. 2022 Oct 3;28(19):4292-4301.
5. Posner A, Prall OW, et. al. A comparison of DNA sequencing and gene expression profiling to assist tissue of origin diagnosis in cancer of unknown primary. J Pathol. 2023 Jan;259(1):81-92. doi: 10.1002/path.6022. Epub 2022 Nov 30. PMID: 36287571; PMCID: PMC10099529.
6. Wang X, Beharry A, Sheffield BS, et al. Feasibility of point-of-care genomic profiling in the diagnosis and treatment of cancer of unknown primary. Oncologist. 2023 Jun 2;28(6):474-478.
7. Krämer A, Bochtler T, et. al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Mar;34(3):228-246. doi: 10.1016/j.annonc.2022.11.013. Epub 2022 Dec 20. PMID: 36563965.
8. Overview of the classification and management of cancers of unknown primary site UpToDate.com/login [via subscription only]. Published March 24, 2025. Updated August 19, 2026. Accessed September 9, 2026.
9. Qi P, et. al. Diagnostic Utility of a 90-Gene Expression Assay (Canhelp-Origin) for Patients with Metastatic Cancer with an Unclear or Unknown Diagnosis. Mol Diagn Ther. 2025 Jan;29(1):81-89. doi: 10.1007/s40291-024-00746-6. Epub 2024 Sep 27. PMID: 39333459.
10. Ghani H, et. al. GPSai: A Clinically Validated AI Tool for Tissue of Origin Prediction during Routine Tumor Profiling. Cancer Res Commun. 2025 Sep 1;5(9):1477-1489. doi: 10.1158/2767-9764.CRC-25-0171. PMID: 40741943; PMCID: PMC12399951.

Approval And Revision History

September 16, 2020: Reviewed by IMPAC, renewed without changes.

Subsequent endorsement date(s) and changes made:

- September 24, 2020: Fax number for Unify updated.
- October 21, 2020: Reviewed by IMPAC, renewed without changes.
- August 18, 2021: Reviewed by IMPAC, renewed without changes.
- October 20, 2021: Reviewed by IMPAC, renewed without changes.
- February 1, 2022: Template Updated
- June 15, 2022: Reviewed by MPAC. Effective October 1, 2022, Medical Necessity Guideline no longer applicable to Tufts Health Together, Tufts Health Direct, Tufts Health Unify and Tufts Health RITogether. AIM Specialty Health® (AIM) will oversee medical necessity review for Tufts Health Public Plans.
- November 16, 2022: Reviewed by MPAC, renewed without changes.
- December 21, 2022: Reviewed at MPAC. For effective date February 1, 2023, CPT code 84999 removed.
- October 18, 2023: reviewed by MPAC, renewed without changes.
- November 2023: Unify name changed to One Care effective January 1, 2024

- November 21, 2024: reviewed by MPAC, renewed without changes, effective January 1, 2025.
- September 17, 2025. Reviewed by MPAC, annual review no changes, effective November 1, 2025. References updated.
- October 21, 2025: Fax number for Senior Care Options, Tufts Medicare Preferred HMO and Tufts Medicare Preferred PPO updated; language for Carelink removed; Harvard Pilgrim Health Care Stride Medicare Advantage removed as an applicable product from the template.
- October 21, 2026. Reviewed by MPAC, annual review no changes. Effective date November 4, 2026.

Background, Product and Disclaimer Information

Medical Necessity Guidelines are developed to determine coverage for benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. We make coverage decisions using these guidelines, along with the Member's benefit document, and in coordination with the Member's physician(s) on a case-by-case basis considering the individual Member's health care needs.

Medical Necessity Guidelines are developed for selected therapeutic or diagnostic services found to be safe and proven effective in a limited, defined population of patients or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in our service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. We revise and update Medical Necessity Guidelines annually, or more frequently if new evidence becomes available that suggests needed revisions.

For self-insured plans, coverage may vary depending on the terms of the benefit document. If a discrepancy exists between a Medical Necessity Guideline and a self-insured Member's benefit document, the provisions of the benefit document will govern. For Tufts Health Together (Medicaid), coverage may be available beyond these guidelines for pediatric members under age 21 under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefits of the plan in accordance with 130 CMR 450.140 and 130 CMR 447.000, and with prior authorization.

Treating providers are solely responsible for the medical advice and treatment of Members. The use of this guideline is not a guarantee of payment, or a final prediction of how specific claim(s) will be adjudicated. Claims payment is subject to eligibility and benefits on the date of service, coordination of benefits, referral/authorization, utilization management guidelines when applicable, and adherence to plan policies, plan procedures, and claims editing logic.