Genomic and Molecular Biomarker Testing for Cancer

Humana
Medicaid Medical Coverage Policy

Original Effective Date: 08/05/2025
Effective Date: 01/16/2026
Review Date: 08/05/2025
Policy Number: HUM-2248-000
Line of Business: Medicaid
States: FL

Table of Contents

HEMATOLOGIC MALIGNANCIES AND SUSPECTED MYELOID DISORDERS
Comprehensive Genomic Profiling/Multigene Panel Testing

Description

Comprehensive genomic profiling (CGP) (also referred to as comprehensive molecular profiling) is a type of test that involves a combination of laboratory methodologies to detect genetic alterations and biomarkers in blood or bone marrow to aid in the management of hematologic malignancies and suspected myeloid disorders. Testing is performed by removing a small sample of tissue for evaluation (eg, bone marrow biopsies, bone marrow aspirates, bone marrow clots), blood draw (peripheral blood samples), or sites located outside of the bone marrow (extramedullary) suspected of harboring a myeloid malignancy. Techniques can vary from test to test and may include but are not limited to, next-generation sequencing (NGS), fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). Examples of CGP tests include, but are not limited to, **FoundationOne Heme and Neogenomics myeloid and/or heme panels.**

Multigene (or expanded) panels analyze a broad set of genes simultaneously (as opposed to single gene testing that searches for variants in one specific gene). Panels often include medically actionable genes but may also include those with unclear medical management. Targeted (or focused) multigene panels analyze a limited number of genes targeted to a specific condition. An example of a multigene panel includes, but may not be limited to, **MyAML Gene Panel Assay**.

Coverage Determination

Comprehensive Genomic Profiling or Multigene Panel Testing for Hematologic Malignancies and Suspected Myeloid Disorders

Humana members may be eligible under the Plan for **comprehensive genomic profiling or multigene panel testing (81450, 81455)** for any of the following indications**:**

- Cancer of the blood and bone marrow (eg, acute myelogenous leukemia [AML])[14]; **OR**
- Myelodysplastic syndrome (MDS)[15]; **OR**
- Myeloproliferative neoplasms (MPNs) which include polycythemia vera (PV), essential thrombocythemia (ET) or primary myelofibrosis (PMF)[16], **OR**
- Suspected myeloid malignancy (does not have a diagnosis of cancer) with undefined cytopenia***** for greater than four months without a known cause[13]; **OR**
- Systemic mastocytosis[18]

*****Clinical, laboratory and pathologic assessment are nondiagnostic (such as demonstration of persistent cytopenias [eg, four months] by complete blood count, microscopic examination of a bone marrow biopsy

and bone marrow cytogenetic studies. Other than the clinical feature of the number of cytopenias and specific cytogenetic changes found recurrently in myelodysplastic syndrome [MDS], all other diagnostic criteria in MDS rely upon light microscopy findings).[13]

Coverage Limitations

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA	
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

References

1. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228.

2. Association for Molecular Pathology (AMP). Clinical significance of DNA variants in chronic myeloid neoplasms: a report of the Association for Molecular Pathology. https://amp.org. Published November 2018.

3. Barbui T, Thiele J, Gisslinger H, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J*. 2018; 8(2):15.

4. ClinicalKey. Clinical Overview. Acute myelogenous leukemia. https://clinicalkey.com. Updated March 10, 2025.

5. ClinicalKey. Clinical Overview. Myelodysplastic syndrome. https://clinicalkey.com. Updated January 1, 2025.

6. College of American Pathologists (CAP). CAP Laboratory Improvement Programs. Initial diagnostic workup of acute leukemia: guideline from the College of American Pathologists and the American Society of Hematology. https://cap.org. Published October 2017.

7. ECRI Institute. ECRIgene. NeoTYPE AML Prognostic Profile (NeoGenomics Laboratories Inc.) for prognosis of acute myeloid leukemia. https://home.ecri.org. Published March 2019.

8. Hayes, Inc. Clinical Utility Evaluation. Genetic testing for the diagnosis and treatment of polycythemia vera (PV). https://evidence.hayesinc.com. Published April 2, 2018. Updated June 17, 2022.

9. Hayes, Inc. Clinical Utility Evaluation. Genetic testing for the diagnosis and treatment monitoring of primary myelofibrosis (PMF). https://evidence.hayesinc.com. Published April 12, 2018. Updated June 17, 2022.

10. Hayes, Inc. GTE Report. Molecular/cytogenetic testing for diagnosis and prognosis in primary/de novo acute myeloid leukemia (AML). https://evidence.hayesinc.com. Published July 24, 2014. Updated July 7, 2015.

11. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*. 2022;36(7):1703-1719.

12. Malcovati L, Galli A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. *Blood*. 2017;129(25):3371-3378.

13. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Acute myeloid leukemia. https://nccn.org. Updated January 27, 2025.

14. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Myelodysplastic syndromes. https://nccn.org. Updated January 17, 2025.

15. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Myeloproliferative neoplasms. https://nccn.org. Updated February 21, 2025.

16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Systemic mastocytosis. https://nccn.org. Updated February 21, 2025.

17. UpToDate, Inc. Acute myeloid leukemia: clinical manifestations, pathologic features, and diagnosis. https://uptodate.com. Updated May 2025.

18. UpToDate, Inc. Clinical manifestations, diagnosis, and classification of myelodysplastic syndromes (MDS). https://uptodate.com. Updated May 2025.

19. UpToDate, Inc. General aspects of cytogenetic analysis in hematologic malignancies. https://uptodate.com. Updated May 2025.

20. Yu J, Li Y, Li T, et al. Gene mutational analysis by NGS and its clinical significance in patients with myelodysplastic syndrome and acute myeloid leukemia. *Exp Hematol Oncol*. 2020;9:2.

21. Zheng G, Chen P, Pallavajjalla A, et al. The diagnostic utility of targeted gene panel sequencing in discriminating etiologies of cytopenia. *Am J Hematol*. 2019;94(10):1141-1148.

HEMATOLOGIC MALIGNANCIES AND SUSPECTED MYELOID DISORDERS
Single Gene Testing

Description

Single gene testing may also be performed for hematologic malignancies and suspected myeloid disorders and may be indicated for an individual who exhibits disease symptoms and may be necessary to diagnose or rule out suspected cancer or monitor known cancer. These include, but are not limited to, *ASXL1, BTK, CCND1, CEBPA, EZH2, IDH1, IDH2, MYD88, NPM1, PLCG2, RUNX1, SF3B1, SRSF2, U2AF1,* and *ZRSR2*.

Coverage Determination

***ASXL1* Gene Testing**

Humana members may be eligible under the Plan for ***ASXL1* gene testing (81175)** for any of the following indications:

- AML (includes acute promyelocytic leukemia [APL]); **OR**
- Blastic plasmacytoid dendritic cell neoplasm (BPDCN); **OR**
- Chronic myeloid leukemia (CML) [13]; **OR**
- Myelodysplastic syndrome (MDS); **OR**
- Myeloproliferative neoplasms (MPN); **OR**
- Suspected myeloid malignancy with undefined cytopenia*****; **OR**
- Systemic mastocytosis

***BTK* Gene Testing**
Humana members may be eligible under the Plan for ***BTK* gene testing** (81233) for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in an individual with disease progression or no response while taking BTK inhibitor therapy including if poor adherence is considered as a possible cause.

***EZH2* Gene Testing**
Humana members may be eligible under the Plan for ***EZH2* gene testing (81236/81237)** for any of the following indications:

- AML (includes APL); **OR**
- Diffuse large b-cell lymphoma; **OR**
- Follicular lymphoma to determine benefit of treatment with tazemetostat (Tazverik) performed with an FDA-approved test; **OR**
- MDS; **OR**
- MPNs

***MYD88* Gene Testing**
Humana members may be eligible under the Plan for ***MYD88* gene testing (81305)** for any of the following indications:

- Extranodal marginal zone B-cell lymphoma of nongastric sites (noncutaneous); **OR**
- Extranodal marginal zone B-cell lymphoma of the stomach; **OR**
- Monoclonal gammopathy of neurological significance (MGNS); **OR**
- Monoclonal gammopathy of renal significance (MGRS); **OR**
- Multiple myeloma; **OR**
- Nodal marginal zone lymphoma; **OR**
- Splenic marginal zone lymphoma; **OR**
- Systemic light chain amyloidosis if lymphoplasmacytic clone is present; **OR**
- Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma

***PLCG2* Gene Testing**
Humana members may be eligible under the Plan for ***PLCG2* gene testing (81233)** for chronic lymphocytic leukemia/small lymphocytic lymphoma in an individual with disease progression or no response while taking BTK inhibitor therapy including if poor adherence is considered as a possible cause.

***SRSF2* Gene Testing**
Humana members may be eligible under the Plan for ***SRSF2* gene testing (81348)** for any of the following indications:

- AML (includes APL); **OR**
- MDS; **OR**
- MPN; **OR**
- Suspected myeloid malignancy with undefined cytopenia*****; **OR**
- Systemic mastocytosis

*****Clinical, laboratory and pathologic assessment are nondiagnostic (such as demonstration of persistent cytopenias [eg, four months] by complete blood count, microscopic examination of a bone marrow biopsy and bone marrow cytogenetic studies. Other than the clinical feature of the number of cytopenias and specific cytogenetic changes found recurrently in myelodysplastic syndrome [MDS], all other diagnostic criteria in MDS rely upon light microscopy findings).

Coverage Limitations

There are no limitations; refer to Coverage Determination Section.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence	
81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)	
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence	
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)	

81305	MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant	
81320	PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

References

1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*. 2022;36(7):1703-1719.

2. National Comprehensive Cancer Network (NCCN). NCCN Biomarkers Compendium. ASXL1, BTK, EZH2, MYD88, PLCG2. https://nccn.org. Updated 2025.

3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Acute lymphoblastic leukemia. https://nccn.org. Updated June 27, 2025.

4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Acute myeloid leukemia. https://nccn.org. Updated January 27, 2025.

5. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. B-cell lymphomas. https://nccn.org. Updated February 10, 2025.

6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma. https://nccn.org. Updated April 2, 2025.

7. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Chronic myeloid leukemia. https://nccn.org. Updated November 27, 2024.

8. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Multiple myeloma. https://nccn.org. Updated June 24, 2025.

9. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Myelodysplastic syndromes. https://nccn.org. Updated January 17, 2025.

10. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Myeloproliferative neoplasms. https://nccn.org. Updated February 21, 2025.

11. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Systemic light chain amyloidosis. https://nccn.org. Updated June 11, 2025.

12. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Systemic mastocytosis. https://nccn.org. Updated February 21, 2025.

13. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma. https://nccn.org. Updated June 24, 2025.

14. US Food & Drug Administration (FDA). Full prescribing information: Tazverik (tazemetostat). https://fda.gov. Published 2020. Updated August 2024.

15. US Food & Drug Administration (FDA). List of cleared or approved companion diagnostic devices (in vitro and imaging tools). https://fda.gov. Updated March 5, 2025.

16. US Food & Drug Administration (FDA). Premarket approval. cobas EZH2 Mutation Test. https://fda.gov. Published June 22, 2020.

Molecular Markers in Fine Needle Aspirates of Thyroid Nodules

Description

Laboratory examination of cells in thyroid nodules acquired through fine needle aspiration (FNA) has been proposed to assist in exploring the possibility of thyroid cancer. These tests are used to detect molecular markers that are associated with thyroid cancer and are performed when cytopathology cannot determine if the nodule is malignant or benign. This classification is referred to as indeterminate.

Thyroid nodules are abnormal growths or lumps that develop in the thyroid gland. While most are benign, a small percentage are malignant. To determine the likelihood of malignancy, FNA is used to obtain cells from the nodule that is evaluated by cytopathology. FNA results are then assigned to one of 5 categories based on a classification system known as The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Results categorized as indeterminate warrant further evaluation, which may include repeat FNA, thyroid surgery and/or histopathology. Even with the additional examinations, most cases are ultimately classified as benign. Testing for molecular markers in specimens already attained via FNA potentially eliminates the need for repeat FNA or for surgery.

Testing for molecular markers in thyroid nodules specimens differs from germline genetic mutation testing. Analysis of molecular markers evaluates specimens for mutations acquired over an individual's

lifetime and are present only in the tissue sampled. Germline DNA is constant and identical in all body tissue types and mutations are inheritable.

Coverage Determination

There are no covered indications; refer to Coverage Limitations Section.

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for **molecular markers in thyroid nodule specimens obtained by FNA** for any indications or tests other than those listed above including, but may not be limited to:

- Use of more than one molecular marker assay

A review of the current medical literature shows that the **evidence is insufficient** to determine that this service is standard medical treatment. There is an absence of current, widely-used treatment guidelines or acceptable clinical literature examining benefit and long-term clinical outcomes establishing the value of this service in clinical management.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

References

1. American Association of Clinical Endocrinologists (AACE). AACE/ACE/AME Guidelines. American Association of Clinical Endocrinology, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules – 2016 update. https://aace.com. Published May 2016.

2. American Association of Clinical Endocrinologists (AACE). White Paper. American Association of Clinical Endocrinology and Associazione Medici Endocrinologi thyroid nodule algorithmic tool. https://aace.com. Published 2021.

3. American Thyroid Association (ATA). American Thyroid Association statement on surgical application of molecular profiling for thyroid nodules: current impact on perioperative decision making. https://thyroid.org. Published July 10, 2015.

4. American Thyroid Association (ATA). Special Articles. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. https://thyroid.org. Published January 12, 2016.

5. Bardet S, Goardon N, Lequesne J, et al. Diagnostic and prognostic value of a 7-panel mutation testing in thyroid nodules with indeterminate cytology: the SWEETMAC study. *Endocrine*. 2021;71(2):407-417.

6. Carr DM, Mastorides S, Stobaugh C, Carlton G, DeLand L, Borkowski A. Molecular testing of atypical thyroid nodules with corresponding surgical correlation: five-year retrospective review in veterans population. *Cureus*. 2022;14(2):e22536.

7. Ciarletto AM, Narick C, Malchoff CD, et al. Analytical and clinical validation of pairwise microRNA expression analysis to identify medullary thyroid cancer in thyroid fine-needle aspiration samples. *Cancer Cytopathol*. 2021;129(3):239-249.

8. ClinicalKey. Clinical Overview. Thyroid nodule. https://clinicalkey.com. Updated January 1, 2024.

9. Craig S, Stretch C, Farshidfar F, et al. A clinically useful and biologically informative genomic classifier for papillary thyroid cancer. *Front Endocrinol (Lausanne)*. 2023:14:1220617.

10. Gallant JN, Chen SC, Ortega CA, et al. Evaluation of the molecular landscape of pediatric thyroid nodules and use of a multigene genomic classifier in children. *JAMA Oncol*. 2022;8(9):1323-1327.

11. Gargano SM, Badjatia N, Nikolaus Y, Peiper SC, Wang ZX. Characterization and clinical significance of EIF1AX mutations and co-mutations in cytologically indeterminate thyroid nodules: a 5-year retrospective analysis. *Acta Med Acad*. 2021;50(1):4-12.

12. Gokozan HN, Dilcher TL, Alperstein SA, et al. Combining molecular testing and the Bethesda category III:VI ratio for thyroid fine-needle aspirates: A quality-assurance metric for evaluating diagnostic performance in a cytopathology laboratory. *Cancer Cytopathol*. 2022;130(4):259-274.

13. Hu C, Jing W, Chang Q, et al. Risk stratification of indeterminate thyroid nodules by novel multigene testing: a study of Asians with a high risk of malignancy. *Mol Oncol*. 2022;16(8):1680-1693.

14. Kaya C, Dorsaint, P, Mercurio S, et al. Limitations of detecting genetic variants from the RNA sequencing data in tissue and fine-needle aspiration samples. *Thyroid*. 2021;31(4):589-595.

15. Kim TH, Jeong DJ, Hahn SY, et al. Triage of patients with AUS/FLUS on thyroid cytopathology: effectiveness of the multimodal diagnostic techniques. *Cancer Med*. 2016;5(5):769-777.

16. Lu SY, Chen YC, Zhu CF, et al. A five-gene panel refines differential diagnosis of thyroid nodules. *J Clin Lab Anal*. 2021;35(9):e23920.

17. Napoli F, Rapa I, Mortara U, et al. MicroRNA profiling predicts positive nodal status in papillary thyroid carcinoma in the preoperative setting. *Cancer Cytopathol*. 2022;130(9):695-704.

18. National Comprehensive Cancer Network (NCCN). NCCN Biomarkers Compendium. Thyroid carcinoma. https://nccn.org. Updated 2025.

19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Thyroid carcinoma. https://nccn.org. Updated March 27, 2025.

20. Schumm MA, Shu ML, Hughes EG, et al. Prognostic value of preoperative molecular testing and implications for initial surgical management in thyroid nodules harboring suspected (Bethesda V) or known (Bethesda VI) papillary thyroid cancer. *JAMA Otolaryngol Head Neck Surg*. 2023;149(8):735-742.

21. Sistrunk JW, Shifrin A, Frager M, et al. Clinical impact of testing for mutations and microRNAs in thyroid nodules. *Diagn Cytopathol*. 2019;47(8):758-764.

22. Skaugen JM, Taneja C, Liu JB, et al. Performance of a multigene genomic classifier in thyroid nodules with suspicious for malignancy cytology. *Thyroid*. 2022;32(12):1500-1508.

23. UpToDate, Inc. Atlas of thyroid cytopathology. https://uptodate.com. Updated June 2025.

24. UpToDate, Inc. Diagnostic approach to and treatment of thyroid nodules. https://uptodate.com. Updated June 2025.

25. UpToDate, Inc. Evaluation and management of thyroid nodules with indeterminate cytology. https://uptodate.com. Updated June 2025.

26. UpToDate, Inc. Oncogenes and tumor suppressor genes in thyroid nodules and nonmedullary thyroid cancer. https://uptodate.com. Updated June 9, 2025.

27. Valderrabano P, Hallanger-Johnson JE, Thapa R, Wang X, McIver B. Comparison of postmarketing findings vs the initial clinical validation findings of a thyroid nodule gene expression classifier: a systematic review and meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2019;e191449.

28. Yip L, Gooding WE, Nikitski A, et al. Risk assessment for distant metastasis in differentiated thyroid cancer using molecular profiling: A matched case-control study. *Cancer*. 2021;127(11):1779-1787.

SOLID TUMORS
Comprehensive Genomic Profiling and Multigene Panel Testing

Description

Comprehensive genomic profiling (CGP) (also referred to as comprehensive molecular profiling or tumor profiling) is a laboratory diagnostic method used to analyze the genetic makeup of solid tumors. CGP examines a wide range of genetic variations including mutations, insertions, deletions, amplifications and rearrangements across hundreds of genes. CGP can help guide targeted treatment options. Some CGP tests analyze DNA to detect genetic alterations. These DNA-based tests focus on identifying somatic mutations which occur in tumor cells and are not inherited. Examples include, but are not limited to, **Guardant360 TissueNext, MSK-IMPACT, Oncotype MAP Pan-Cancer Tissue Test and PGDx elio tissue complete**.

Coverage Determination

Comprehensive Genomic Profiling

Humana members may be eligible under the Plan for **comprehensive genomic profiling for solid tumors** for any of the following tests when the criteria below are met:

- Oncotype MAP PanCancer Tissue Test (0244U)

AND both of the following:

- Individual to be tested has been diagnosed with recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; **AND**

- Individual has decided to seek further cancer treatment (eg, therapeutic chemotherapy)

Coverage Limitations

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

References

1. American Academy of Dermatology (AAD). Guidelines of care for the management of primary cutaneous melanoma. https://aad.org. Published January 2019.

2. American College of Medical Genetics and Genomics (ACMG). ACMG Technical Standard. Section E6.7-6.12 of the American College of Medical Genetics and Genomics (ACMG) Technical Laboratory Standards: cytogenomic studies of acquired chromosomal abnormalities in solid tumors. https://acmg.net. Published 2024.

3. American Society of Clinical Oncology (ASCO). Biomarkers for systemic therapy in metastatic breast cancer guideline and rapid update. https://asco.org. Updated February 6, 2024.

4. American Society of Clinical Oncology (ASCO). Endocrine treatment and targeted therapy for HR-positive, HER2-negative metastatic breast cancer guideline and rapid update. https://asco.org. Published February 22, 2016. Updated February 18, 2025.

5. American Society of Clinical Oncology (ASCO). Germline and somatic genomic testing for metastatic prostate cancer: ASCO guideline. https://asco.org. Published January 9, 2025.

6. American Society of Clinical Oncology (ASCO). Immunotherapy and biomarker testing in recurrent and metastatic head and neck cancers: ASCO guideline. https://asco.org. Published December 15, 2022.

7. American Society of Clinical Oncology (ASCO). Metastatic pancreatic cancer: ASCO guideline update. https://asco.org. Published August 5, 2020.

8. American Society of Clinical Oncology (ASCO). Mismatch repair and microsatellite instability testing for immune checkpoint inhibitor therapy: ASCO endorsement of College of American Pathologists guideline. https://asco.org. Published January 5, 2023.

9. American Society of Clinical Oncology (ASCO). Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the study of lung cancer/association for molecular pathology clinical practice guideline update. https://asco.org. Published February 5, 2018.

10. American Society of Clinical Oncology (ASCO). Poly (ADP-ribose) polymerase inhibitors in the management of ovarian cancer: ASCO guideline rapid recommendation update. https://asco.org. Published August 25, 2022.

11. American Society of Clinical Oncology (ASCO). Somatic genomic testing in patients with metastatic or advanced cancer: ASCO provisional clinical opinion. https://asco.org. Published February 10, 2022. Updated February 24, 2025.

12. American Society of Clinical Oncology (ASCO). Treatment of metastatic colorectal cancer: ASCO guideline. https://asco.org. Published October 17, 2022.

13. American Society of Clinical Oncology (ASCO). Treatment of pleural mesothelioma: ASCO guideline update. https://asco.org. Published January 8, 2025.

14. American Thyroid Association (ATA). 2021 American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer: American Thyroid Association Anaplastic Thyroid Cancer Guidelines Task Force. https://thyroid.org. Published 2021.

15. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Biliary tract cancers. https://nccn.org. Updated January 10, 2025.

16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Bladder cancer. https://nccn.org. Updated January 17, 2025.

17. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast cancer. https://nccn.org. Updated April 17, 2025.

18. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Central nervous system cancers. https://nccn.org. Updated January 21, 2025.

19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Colon cancer. https://nccn.org. Updated April 24, 2025.

20. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. https://nccn.org. Updated January 14, 2025.

21. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Occult primary (cancer of unknown primary [CUP]). https://nccn.org. Updated September 11, 2024.

22. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. https://nccn.org. Updated July 16, 2025.

23. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Pancreatic adenocarcinoma. https://nccn.org. Updated December 20, 2024.

24. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Prostate cancer. https://nccn.org. Updated December 4, 2024.

25. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Rectal cancer. https://nccn.org. Updated March 31, 2025.

26. UpToDate, Inc. Adenocarcinoma of unknown primary site. https://uptodate.com. Updated January 2025.

27. UpToDate, Inc. Initial systemic therapy for advanced non-small cell lung cancer lacking a driver mutation. https://uptodate.com. Updated January 2025.

28. UpToDate, Inc. Initial systemic therapy for metastatic colorectal cancer. https://uptodate.com. Updated January 21, 2025.

29. UpToDate, Inc. Management of advanced prostate cancer with germline or somatic homologous recombination repair deficiency. https://uptodate.com. Updated January 2025.

30. UpToDate, Inc. Management of ovarian cancer associated with BRCA and other genetic mutations. https://uptodate.com. Updated January 2025.

31. UpToDate, Inc. Medical treatment for relapsed epithelial ovarian, fallopian tubal, or peritoneal cancer: platinum-resistant disease. https://uptodate.com. Updated January 2025.

32. UpToDate, Inc. Overview of the approach to metastatic breast cancer. https://uptodate.com. Updated January 2025.

33. UpToDate, Inc. Overview of the initial treatment of advanced non-small cell lung cancer. https://uptodate.com. Updated January 2025.

34. UpToDate, Inc. Pathology and prognostic determinants of colorectal cancer. https://uptodate.com. Updated January 2025.

35. UpToDate, Inc. Personalized, genotype-directed therapy for advanced non-small cell lung cancer. https://uptodate.com. Updated January 22, 2025.

36. UpToDate, Inc. Prognostic and predictive factors in metastatic breast cancer. https://uptodate.com. Updated August 2024.

37. UpToDate, Inc. Treatment for hormone receptor-positive, HER2-negative advanced breast cancer. https://uptodate.com. Updated January 31, 2025.

38. UpToDate, Inc. Treatment of metastatic breast cancer in older women. https://uptodate.com. Updated August 2024.

SOLID TUMORS
Single Gene Testing

Description

Single gene tests analyze only one gene for variants specific to cancer type. Examples of single gene tests include *PIK3CA* and *TERT.*

Coverage Determination

***PIK3CA* Gene Testing**
Humana members may be eligible under the Plan for ***PIK3CA* gene testing (81309)** for the following indications:

- Breast cancer – advanced or metastatic; **AND**
    - Disease progression on or after endocrine-based therapy; **AND**
    - HR-positive and HER2-negative disease; **AND**
    - Test is FDA approved; **AND**
    - To determine eligibility for treatment with either of the following:
        - Alpelisib (Piqray) in combination with fulvestrant (Faslodex); **OR**
        - Inavolisib (Itovebi) in combination with palbociclib (Ibrance) and fulvestrant (Faslodex); **OR**

- Breast cancer; **AND**

  - Disease progression on or after endocrine-based therapy; **AND**
  - HR-positive and HER2-negative disease; **AND**
  - To determine eligibility for treatment with alpelisib (Piqray) in combination with fulvestrant (Faslodex)

***TERT* Gene Testing**

Humana members may be eligible under the Plan for ***TERT* gene testing (81345)** for the following indications:

- Glioma; **OR**
- Melanoma, cutaneous; **OR**
- Uterine carcinoma

Coverage Limitations

There are no limitations; refer to Coverage Determination Section.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)	
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

References

1. American Academy of Dermatology (AAD). Guidelines of care for the management of primary cutaneous melanoma. https://aad.org. Published January 2019.

2. American Society of Clinical Oncology (ASCO). Biomarkers for systemic therapy in metastatic breast cancer guideline and rapid update. https://asco.org. Updated February 6, 2024.

3. American Society of Clinical Oncology (ASCO). Somatic genomic testing in patients with metastatic or advanced cancer: ASCO provisional clinical opinion. https://asco.org. Published February 17, 2022.

4. College of American Pathologists (CAP). Molecular biomarker testing for the diagnosis of diffuse gliomas: guideline from the College of American Pathologists in collaboration with the American Association of Neuropathologists, Association for Molecular Pathology, and Society for Neuro-Oncology. https://cap.org. Published May 2022.

5. National Comprehensive Cancer Network (NCCN). NCCN Biomarkers Compendium: PIK3CA, TERT. https://nccn.org. Updated 2025.

6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast cancer. https://nccn.org. Updated March 18, 2025.

7. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Central nervous system cancers. https://nccn.org. Updated January 21, 2025.

8. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. https://nccn.org. Updated January 28, 2025.

9. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Uterine neoplasms. https://nccn.org. Updated March 7, 2025.

10. Society for Immunotherapy of Cancer (SITC). Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of breast cancer. https://sitcancer.org. Published August 13, 2021.

11. UpToDate, Inc. Classification and pathologic diagnosis of gliomas, glioneuronal tumors, and neuronal tumors. https://uptodate.com. Updated January 2025.

12. UpToDate, Inc. Clinical features, diagnosis, and pathology of IDH-mutant, 1p/19q-codeleted oligodendrogliomas. https://uptodate.com. Updated January 2025.

13. UpToDate, Inc. Initial treatment and prognosis of IDH-wildtype glioblastoma in adults. https://uptodate.com. Updated January 2025.

14. UpToDate, Inc. Management of glioblastoma in older adults. https://uptodate.com. Updated January 21, 2025.

15. UpToDate, Inc. Melanoma: clinical features and diagnosis. https://uptodate.com. Updated January 2025.

16. UpToDate, Inc. Overview of the approach to metastatic breast cancer. https://uptodate.com. Updated January 2025.

17. UpToDate, Inc. Overview of the management of advanced cutaneous melanoma. https://uptodate.com. Updated January 2025.

18. UpToDate, Inc. Principles of cancer immunotherapy. https://uptodate.com. Updated January 2025.

19. UpToDate, Inc. Prognostic and predictive factors in metastatic breast cancer. https://uptodate.com. Updated January 2025.

20. UpToDate, Inc. Systemic treatment of metastatic melanoma with BRAF and other molecular alterations. https://uptodate.com. Updated January 2025.

21. UpToDate, Inc. Treatment for hormone receptor-positive, HER2-negative advanced breast cancer. https://uptodate.com. Updated January 31, 2025.

22. UpToDate, Inc. Treatment of metastatic breast cancer in older women. https://uptodate.com. Updated August 2024.

23. US Food & Drug Administration (FDA). Full prescribing information: Faslodex (fulvestrant). https://fda.gov. Published 2002. Updated January 2021.

24. US Food & Drug Administration (FDA). Full prescribing information: Ibrance (palbociclib). https://fda.gov. Published 2015. Updated December 2024.

25. US Food & Drug Administration (FDA). Full prescribing information: Itovebi (inavolisib)). https://fda.gov. Published 2024. Updated January 2025.

26. US Food & Drug Administration (FDA). Full prescribing information: Piqray (alpelisib). https://fda.gov. Published 2019. Updated January 2024.

27. US Food & Drug Administration (FDA). In vitro companion diagnostic devices. https://fda.gov. Published August 6, 2014.

28. US Food & Drug Administration (FDA). Laboratory developed tests. https://fda.gov. Updated October 30, 2024.

29. US Food & Drug Administration (FDA). List of cleared or approved companion diagnostic devices (in vitro and imaging tools). https://fda.gov. Updated 2025.

30. US Food & Drug Administration (FDA). Premarket approval. therascreen PIK3CA RGQ PCR Kit. https://fda.gov. Published May 24, 2019.

Tumor Markers

Description

A **tumor marker** is a protein, antibody, antigen or hormone in the body that may indicate the presence of cancer. Generally, these markers are specific to certain types of cancer and can be detected in blood, body fluids (eg, cerebral spinal fluid [CSF]), stool, tissue and urine samples. The body may produce the marker in response to cancer or the tumor itself may produce the marker. The detection of tumor markers may be used to determine a diagnosis or as an indicator of disease (cancer) progression. It can also be used to document clinical response to treatment. Examples of tumor markers include, but are not limited to:

- **Human epididymis protein 4 (HE4) (eg, Elecsys HE4 Assay)** has been proposed to aid in the detection and monitoring of ovarian cancer.

Coverage Determination

Human Epididymis Protein 4 (HE4)
Humana members may be eligible under the Plan for **human epididymis protein 4 (HE4) testing (86305)** for the following indications:

- Newly diagnosed ovarian, fallopian tube or primary peritoneal cancer; **OR**
- Suspicious palpable pelvic mass on abdomen/pelvis examination; **AND/OR**
- Ascites, abdominal distention; **AND/OR**
- Symptoms without source of malignancy (eg, bloating, difficulty eating or feeling full quickly, pelvis/ abdomen pain, urinary symptoms [frequency or urgency])

Coverage Limitations

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
86305	Human epididymis protein 4 (HE4)	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

References

1. American Society of Clinical Oncology (ASCO). Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: ASCO guideline update. https://asco.org. Published August 4, 2016. Updated February 6, 2025.

2. Hayes, Inc. Medical Technology Directory. Architect HE4 assay for ovarian cancer detection. https://evidence.hayesinc.com. Published December 30, 2012. Updated December 5, 2016.

3. National Comprehensive Cancer Network (NCCN). NCCN Biomarkers Compendium. HE4 expression. https://nccn.org. Updated 2025.

4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. https://nccn.org. Updated March 5, 2025.

5. UpToDate, Inc. Adnexal mass: evaluation and management in pregnancy. https://uptodate.com. Updated March 14, 2025.

6. UpToDate, Inc. Adnexal mass: role of serum biomarkers in diagnosing epithelial carcinoma of the ovary, fallopian tube, or peritoneum. https://uptodate.com. Updated March 2025.

7. UpToDate, Inc. Approach to the patient with an adnexal mass. https://uptodate.com. Updated March 2025.

8. UpToDate, Inc. Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: clinical features and diagnosis. https://uptodate.com. Updated March 2025.

9. UpToDate, Inc. Screening for ovarian cancer. https://uptodate.com. Updated March 2025.

10. US Food & Drug Administration (FDA). 510k summary: Architect HE4. https://fda.gov. Published March 18, 2010.

Change Summary

08/05/2025 New Policy.