

Gene Expression Profiling for Cancer Indications

Humana

Medicaid Medical Coverage Policy

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Description

Gene expression profiling (GEP) is a laboratory test that measures the activity, or expression, of ribonucleic acid (RNA) of hundreds to thousands of genes at one time to give an overall picture of gene activity. GEP tests are typically performed on tumor tissue but may also be performed on other specimens such as blood. These tests often use microarray technology though other methodologies, such as next generation sequencing (NGS), whole transcriptome sequencing and reverse transcription polymerase chain reaction (RT-PCR) are also used.

GEP tests are currently offered primarily for the management of cancer, most notably breast. Other cancer indications include bladder, colon, cancer of unknown primary (CUP), cutaneous (skin) melanoma, cutaneous squamous cell cancer (SCC), hematologic malignancies, lung cancer, oral cancer, pancreatic cancer, prostate cancer and uveal melanoma.

GEP tests differ from germline genetic tests. GEP tests analyze RNA which is dynamic, responds to cellular environmental signals, are not usually representative of an individual's germline DNA and are not inheritable. Germline genetic testing analyzes an individual's deoxyribonucleic acid (DNA) to detect genetic variants (mutations). Germline mutations are inherited, are constant throughout an individual's lifetime and are identical in every cell of the body.

Coverage Determination

PROSTATE CANCER

ConfirmMDx

Humana members may be eligible under the Plan for **ConfirmMDx (81551)** to manage prostate biopsy results when any of the following indications are met⁴⁶:

- Atypia, suspicious for cancer; **OR**
- Benign but clinical suspicion of cancer persists; **OR**
- High-grade prostatic intraepithelial neoplasia (PIN)

ExoDx Prostate Test or MyProstateScore 2.0

Humana members may be eligible under the Plan for **ExoDx Prostate Test (also known as ExoDx Prostate IntelliScore [EPI]) (0005U) or MyProstateScore 2.0 (MPS2) (0403U)** when the following criteria are met⁴⁶:

- Test performed after repeat PSA and digital rectal exam (DRE), and prior to initial biopsy; **AND**
 - Individual is 45 – 75 years of age with PSA between 3ng/mL and 10 ng/mL and/or very suspicious DRE; **OR**
 - Individual is more than 75 years of age with PSA between 4 ng/mL and 10 ng/mL or very suspicious DRE; **OR**
- Test performed to manage biopsy results when any of the following indications are present:
 - Atypia, suspicious for cancer; **OR**
 - Benign but clinical suspicion of cancer persists; **OR**
 - High-grade prostatic intraepithelial neoplasia (PIN)

UVEAL MELANOMA

DecisionDx-UM

Humana members may be eligible under the Plan for **DecisionDx-UM (81552)** for risk stratification in an individual diagnosed with uveal melanoma.

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for the following **gene expression profiling tests**:

- Cancer of unknown primary (CUP) (also referred to as TOO or tumor of unknown origin) (81540)
- Cxbladder Detect (0012M)
- Cxbladder Monitor (0013M)
- Cxbladder Triage (0363U)

- Cxbladder Triage Plus (0420U)
- Decipher Bladder TURBT (0016M)
- DecisionDx-Melanoma (81529)
- DecisionDx-SCC (0315U)
- DetermaRx (0288U)
- EarlyTect Bladder Cancer Detection (EarlyTect BCD) (0452U)
- Genomic Prostate Score (formerly Oncotype DX Genomic Prostate Score) (0047U)
- myPath Melanoma (0090U)
- Oncotype DX Colon Recurrence Score Test (81525)
- PancreaSeq Genomic Classifier (0313U)
- Pigmented Lesion Assay (0089U)

A review of the current medical literature shows that the **evidence is insufficient** to determine that these services are standard medical treatments. There is an absence of current, widely-used treatment guidelines or acceptable clinical literature (as defined by CMS) examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

Humana members may **NOT** be eligible under the Plan for the following **gene expression profiling tests**:

- BBDRisk Dx IHC (0067U)
- CancerDetect (0296U)
- DarwinOncoTarget (formerly known as OncoTarget) and DarwinOncoTreat (formerly known as OncoTreat) (0019U)
- Insight TNBCtype (0153U)
- Lymph2Cx (0017M)
- Lymph3Cx (0120U)
- miR-31now (0069U)
- OncoSignal-7 Pathway (0262U)

A review of the current medical literature shows that there is **no evidence** to determine that these services are standard medical treatments. There is an absence of current, widely-used treatment guidelines or acceptable clinical literature (as defined by CMS) examining benefit and long-term clinical outcomes establishing the value of these services 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
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores	
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score	
81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis	
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy	
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis	
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score	
0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma	
0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma	
0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)	

0017M	Oncology (diffuse large B-cell lymphoma [DLBCL]), mRNA, gene expression profiling by fluorescent probe hybridization of 20 genes, formalin-fixed paraffin-embedded tissue, algorithm reported as cell of origin	
0019U	Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents	
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score	
0067U	Oncology (breast), immunohistochemistry, protein expression profiling of 4 biomarkers (matrix metalloproteinase-1 [MMP-1], carcinoembryonic antigen-related cell adhesion molecule 6 [CEACAM6], hyaluronoglucosaminidase [HYAL1], highly expressed in cancer protein [HEC1]), formalin-fixed paraffin-embedded precancerous breast tissue, algorithm reported as carcinoma risk score	
0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score	
0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)	
0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant)	
0120U	Oncology (B-cell lymphoma classification), mRNA, gene expression profiling by fluorescent probe hybridization of 58 genes (45 content and 13 housekeeping genes), formalin-fixed paraffin-embedded tissue, algorithm reported as likelihood for primary mediastinal B-cell lymphoma (PMBCL) and diffuse large B-cell lymphoma (DLBCL) with cell of origin subtyping in the latter	
0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement	

0262U	Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score	
0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score	
0296U	Oncology (oral and/or oropharyngeal cancer), gene expression profiling by RNA sequencing at least 20 molecular features (eg, human and/or microbial mRNA), saliva, algorithm reported as positive or negative for signature associated with malignancy	
0313U	Oncology (pancreas), DNA and mRNA next-generation sequencing analysis of 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (ie, negative, low probability of neoplasia or positive, high probability of neoplasia)	
0315U	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (ie, Class 1, Class 2A, Class 2B)	
0363U	Oncology (urothelial), mRNA, gene- expression profiling by realtime quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma	
0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch post-digital rectal examination urine (or processed first-catch urine), algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer	
0420U	Oncology (urothelial), mRNA expression profiling by real-time quantitative PCR of MDK, HOXA13, CDC2, IGFBP5, and CXCR2 in combination with droplet digital PCR (ddPCR) analysis of 6 single-nucleotide polymorphisms (SNPs) genes TERT and FGFR3, urine, algorithm reported as a risk score for urothelial carcinoma	
0452U	Oncology (bladder), methylated PENK DNA detection by linear target enrichment-quantitative methylation-specific real-time PCR (LTE-qMSP), urine, reported as likelihood of bladder cancer	
CPT® Category III Code(s)	Description	Comments

No code(s) identified		
HCPCS Code(s)	Description	Comments
S3854	Gene expression profiling panel for use in the management of breast cancer treatment	

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 Gastroenterology (ACG). ACG clinical guideline: diagnosis and management of pancreatic cysts. <https://gi.org>. Published February 2018.
3. American Society of Colon and Rectal Surgeons (ASCRS). Clinical Practice Guidelines. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the management of colon cancer. <https://fascrs.org>. Published 2022.
4. American Urological Association (AUA). Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. <https://auanet.org>. Published April 2016. Updated 2024.
5. American Urological Association (AUA). Early detection of prostate cancer: AUA/SUO guideline. <https://auanet.org>. Published 2023.
6. American Urological Association (AUA). Microhematuria: AUA/SUFU guideline. <https://auanet.org>. Published 2020. Updated 2025.
7. ECRI Institute. ECRIgene Genetic Test Product Brief. DecisionDx-UM (Castle Biosciences, Inc.) for assessing metastatic risk in patients with uveal melanoma. <https://home.ecri.org>. Published April 2017.
8. ECRI Institute. ECRIgene Genetic Test Product Brief. Oncotype DX Colon Cancer Assay (Genomic Health, Inc.) for evaluating prognosis and predicting response to chemotherapy. <https://home.ecri.org>. Published March 2018.
9. ECRI Institute. ECRIgene Genetic Test Product Brief. Oncotype DX Genomic Prostate Score (Genomic Health, Inc.) for assessing prostate cancer prognosis. <https://home.ecri.org>. Published April 2020.
10. ECRI Institute. Genetic Test Assessment. CancerTYPE ID (bioTheranostics, Inc.) to aid in determining tumor type of cancers of unknown primary origin. <https://home.ecri.org>. Published September 2021.
11. ECRI Institute. Genetic Test Assessment. ConfirmMDx (MDxHealth) for determining need for repeat biopsy. <https://home.ecri.org>. Published August 2022.

12. ECRI Institute. Genetic Test Assessment. Cxbladder Detect (Pacific Edge, Ltd.) urine test to aid diagnosis of urothelial carcinoma. <https://home.ecri.org>. Published June 2021.
13. ECRI Institute. Genetic Test Assessment. Cxbladder Monitor Test (Pacific Edge, Ltd.) for monitoring urothelial carcinoma recurrence. <https://home.ecri.org>. Published October 2021.
14. ECRI Institute. Genetic Test Assessment. Cxbladder Triage (Pacific Edge, Ltd.) liquid biopsy test to exclude the likelihood of bladder cancer. <https://home.ecri.org>. Published April 2025.
15. ECRI Institute. Genetic Test Assessment. DecisionDx-Melanoma (Castle Biosciences, Inc.) for evaluating prognosis and guiding management of cutaneous melanoma. <https://home.ecri.org>. Published October 2023.
16. ECRI Institute. Genetic Test Assessment. DecisionDx-SCC (Castle Biosciences, Inc.) for evaluating prognosis and guiding management of squamous cell carcinoma. <https://home.ecri.org>. Published May 2022.
17. ECRI Institute. Genetic Test Assessment. DetermaRx (Oncocyte Corp.) for evaluating prognosis of early-stage lung cancer. <https://home.ecri.org>. Published July 2022.
18. ECRI Institute. Genetic Test Assessment. ExoDx Prostate (IntelliScore; Exosome Diagnostics, Inc.) for assessing risk of aggressive prostate cancer. <https://home.ecri.org>. Published December 2023.
19. ECRI Institute. Genetic Test Assessment. myPath Melanoma for aiding diagnosis of melanoma. <https://home.ecri.org>. Published May 2022.
20. ECRI Institute. Genetic Test Assessment. PancreaSeq Genome Classifier (University of Pittsburgh Medical Center) for evaluating pancreatic cysts. <https://home.ecri.org>. Published June 2024.
21. ECRI Institute. Genetic Test Assessment. Pigmented Lesion Assay (PLA) (DermTech) for aiding diagnosis of melanoma. <https://home.ecri.org>. Published March 2023.
22. Hayes, Inc. Molecular Test Assessment. CancerTYPE ID (bioTheranostics Inc.). <https://evidence.hayesinc.com>. Published July 30, 2018. Updated March 25, 2022.
23. Hayes, Inc. Molecular Test Assessment. Confirm mdx (Mdxhealth Inc). <https://evidence.hayesinc.com>. Published February 15, 2024. Updated March 20, 2025.
24. Hayes, Inc. Molecular Test Assessment. Cxbladder Detect (Pacific Edge Ltd.). <https://evidence.hayesinc.com>. Published August 24, 2023. Updated August 28, 2024.
25. Hayes, Inc. Molecular Test Assessment. Cxbladder Monitor (Pacific Edge Ltd.). <https://evidence.hayesinc.com>. Published August 7, 2023. Updated August 29, 2024.

26. Hayes, Inc. Molecular Test Assessment. Cxbladder Triage (Pacific Edge Ltd.). <https://evidence.hayesinc.com>. Published October 26, 2023. Updated November 22, 2024.
27. Hayes, Inc. Molecular Test Assessment. DecisionDx-Melanoma. <https://evidence.hayesinc.com>. Published March 29, 2022. Updated February 27, 2024.
28. Hayes, Inc. Molecular Test Assessment. DecisionDx-SCC (Castle Biosciences Inc.). <https://evidence.hayesinc.com>. Published April 16, 2025.
29. Hayes, Inc. Molecular Test Assessment. DecisionDx-UM (Castle Biosciences Inc.). <https://evidence.hayesinc.com>. Published March 10, 2025.
30. Hayes, Inc. Molecular Test Assessment. ExoDx Prostate Test (Exosome Diagnostics Inc.). <https://evidence.hayesinc.com>. Published April 27, 2023. Updated June 14, 2024.
31. Hayes, Inc. Molecular Test Assessment. Genomic Prostate Score (Mdxhealth Inc.) for higher-risk prostate cancers. <https://evidence.hayesinc.com>. Published July 19, 2024.
32. Hayes, Inc. Molecular Test Assessment. Genomic Prostate Score (Mdxhealth Inc.) for lower-risk prostate cancers. <https://evidence.hayesinc.com>. Published August 27, 2024.
33. Hayes, Inc. Molecular Test Assessment. myPath Melanoma (Castle Biosciences Inc.). <https://evidence.hayesinc.com>. Published February 19, 2025.
34. Hayes, Inc. Molecular Test Assessment. Oncotype DX Colon Recurrence Score (Exact Sciences). <https://evidence.hayesinc.com>. Published June 21, 2024.
35. Hayes, Inc. Molecular Test Assessment. Pigmented Lesion Assay (PLA). <https://evidence.hayesinc.com>. Published September 26, 2019. Updated June 14, 2022.
36. Hayes, Inc. Precision Medicine Research Brief. CancerTYPE ID (Biotheranostics Inc.). <https://evidence.hayesinc.com>. Published April 24, 2023.
37. Hayes, Inc. Precision Medicine Research Brief. DetermaRx (Oncocyte Corporation). <https://evidence.hayesinc.com>. Published November 14, 2022.
38. Hayes, Inc. Precision Medicine Research Brief. PancreaSeq Genomic Classifier (University of Pittsburgh Medical Center). <https://evidence.hayesinc.com>. Published May 20, 2024.
39. National Comprehensive Cancer Network (NCCN). NCCN Biomarkers Compendium. ConfirmMDx, ExoDx Prostate (IntelliScore)(EPI), melanoma: uveal, MyProstateScore. <https://nccn.org>. Updated 2025.
40. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Bladder cancer. <https://nccn.org>. Updated March 25, 2025.

41. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Colon cancer. <https://nccn.org>. Updated April 24, 2025.
42. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. <https://nccn.org>. Updated January 28, 2025.
43. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Melanoma: uveal. <https://nccn.org>. Updated February 11, 2025.
44. 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.
45. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Prostate cancer. <https://nccn.org>. Updated April 16, 2025.
46. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Prostate cancer early detection. <https://nccn.org>. Updated March 11, 2025.
47. Society of Surgical Oncology (SSO). Society of Surgical Oncology consensus statement: assessing the evidence for and utility of gene expression profiling of primary cutaneous melanoma. <https://surgonc.org>. Published 2024.
48. UpToDate, Inc. Active surveillance for males with clinically localized prostate cancer. <https://uptodate.com>. Updated April 2025.
49. UpToDate, Inc. Adenocarcinoma of unknown primary site. <https://uptodate.com>. Updated April 2025.
50. UpToDate, Inc. Adjuvant therapy for resected stage II colon cancer. <https://uptodate.com>. Updated April 2025.
51. UpToDate, Inc. Diffuse large B cell lymphoma and other large B cell lymphomas: presentation, diagnosis, and classification. <https://uptodate.com>. Updated May 6, 2025.
52. UpToDate, Inc. Evaluation of hematuria. <https://uptodate.com>. Updated April 28, 2025.
53. UpToDate, Inc. Initial management of uveal and conjunctival melanomas. <https://uptodate.com>. Updated April 2025.
54. UpToDate, Inc. Localized prostate cancer: risk stratification and choice of initial treatment. <https://uptodate.com>. Updated April 2025.
55. UpToDate, Inc. Melanoma: clinical features and diagnosis. <https://uptodate.com>. Updated April 2025.

56. UpToDate, Inc. Molecular prognostic tests for prostate cancer. <https://uptodate.com>. Updated April 2025.
57. UpToDate, Inc. Neoadjuvant therapy for localized muscle-invasive urothelial carcinoma of the bladder. <https://uptodate.com>. Updated April 2, 2025.
58. UpToDate, Inc. Overview of the classification and management of cancers of unknown primary site. <https://uptodate.com>. Updated April 2025.
59. UpToDate, Inc. Pathologic characteristics of melanoma. <https://uptodate.com>. Updated April 2025.
60. UpToDate, Inc. Pathology and prognostic determinants of colorectal cancer. <https://uptodate.com>. Updated April 2025.
61. UpToDate, Inc. Poorly differentiated cancer of unknown primary site. <https://uptodate.com>. Updated April 2025.
62. UpToDate, Inc. Prognosis of diffuse large B cell lymphoma. <https://uptodate.com>. Updated April 2025.
63. UpToDate, Inc. Prostate biopsy. <https://uptodate.com>. Updated April 2025.
64. UpToDate, Inc. Recognition and management of high-risk (aggressive) cutaneous squamous cell carcinoma. <https://uptodate.com>. Updated April 2025.
65. UpToDate, Inc. Screening for bladder cancer. <https://uptodate.com>. Updated April 2025.
66. UpToDate, Inc. Urine biomarkers for the detection of urothelial (transitional cell) carcinoma of the bladder. <https://uptodate.com>. Updated April 2025.

Change Summary

06/03/2025 New Policy.