# Gene Expression Profiling

Humana

## Medical Coverage Policy

**Effective Date:** 10/22/2020
**Revision Date:** 10/22/2020
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**Change Summary:** Updated Description, Coverage Limitations, Provider Claims Codes, Medical Terms, References

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### Disclaimer



### 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 are also possible. GEP tests are used to determine prognosis, refine risk stratification and/or optimize treatment regimens primarily for cancer, most notably, breast.

**GEP tests differ from genetic tests**. Genetic testing, also known as germline mutation testing, analyzes an individual's deoxyribonucleic acid (DNA) and can identify genetic mutations to determine inherited risk of disease. An individual's germline DNA is constant and identical in all body tissue types. RNA activity is

measured by gene expression analysis. It is dynamic and responds to cellular environmental signals. Mutation analysis of tumor tissue determines DNA mutations that have been acquired over an individual's lifetime. These DNA changes are present only in the tissue sampled, are not usually representative of an individual's germline DNA and are not inheritable.

Examples of GEP for breast cancer include, but may not be limited to:

- BBDRisk Dx (Refer to Coverage Limitations section)
- Breast cancer index (BCI) (Refer to Coverage Limitations section)
- EndoPredict (EPclin)
- Insight TNBC Type (Refer to Coverage Limitations section)
- MammaPrint breast cancer recurrence signature (Refer to Coverage Limitations section)
- Oncotype DX breast cancer assay
- Oncotype DX DCIS (Refer to Coverage Limitations section)
- Prosigna Breast Cancer Prognostic Gene Signature Assay (also known as PAM50 risk of recurrence score)

80-gene molecular subtyping (ie, BluePrint) classifies breast cancer into molecular subtypes (ie, luminal types A and B, HER2 type or basal type) to purportedly provide information regarding chemotherapy or hormone therapy resistance for treatment decision making. **(Refer to Coverage Limitations section)**

Gene expression profiling has also been proposed for determining ER, PR and HER2 status for breast cancer (eg, TargetPrint). **(Refer to Coverage Limitations section)**

For information regarding **HER2 testing,** please refer to Pharmacogenomics and Companion Diagnostics Medical Coverage Policy.

Other proposed cancer indications include, but may not be limited to:

- B-cell lymphoma subtyping classification including primary mediastinal B-cell lymphoma and diffuse large B-cell lymphoma (ie, Lymph3Cx Lymphoma Molecular Subtyping Assay) **(Refer to Coverage Limitations section)**

- Bladder cancer (eg, Cxbladder Detect, Cxbladder Monitor, Cxbladder Triage, Decipher Bladder, Decipher Bladder TURBT) **(Refer to Coverage Limitations Section)**

- Cancer of unknown primary (CUP) (eg, CancerTYPE ID, RosettaGX Cancer Origin, Tissue of Origin [TOO], ResponseDX Tissue of Origin) (~~**NOTE:**~~ Gene expression assays for CUP may also be referred to as molecular cancer classifier assays [MCCAs]) **(Refer to Coverage Limitations section)**

- Colon (eg, ColoPrint, GeneFx Colon Cancer Gene Signature, miR-31now, Oncotype DX for Colon) **(Refer to Coverage Limitations section)**

- Lung (eg, GeneFx Lung, HistoPlus, myPlan Lung Cancer test, Percepta Bronchial Genomic Classifier) **(Refer to Coverage Limitations section)**

- Melanoma, cutaneous or uveal (eg, DecisionDx-Melanoma, DecisionDx-UM, myPath melanoma, Pigmented Lesion Assay [PLA], Uveal Melanoma Prognostic Test) **(Refer to Coverage Limitations section)**

- Whole transcriptome sequencing (ie, OncoTarget/OncoTreat) **(Refer to Coverage Limitations section)**

For information regarding **GEP for prostate cancer** (ie, ConfirmMDx for Prostate Cancer, Decipher Prostate, Oncotype DX Prostate, PCA3, Prolaris), please refer to Laboratory Analysis for Prostate Cancer Medical Coverage Policy.

GEP has also been suggested for noncancer indications, such as idiopathic pulmonary fibrosis (ie, Envisia Genomic Classifier) **(Refer to Coverage Limitations section)**

## Coverage Determination

**Breast Cancer**

Humana members may be eligible under the Plan for **12-gene expression assay for breast cancer** (**EndoPredict [EPclin]) OR 21-gene recurrence score assay (ie, Oncotype DX Breast)** for management of breast cancer when the following criteria are met:

- Breast cancer newly diagnosed in female or male; **AND**
- Breast tumor is estrogen-receptor (ER) positive; **AND**
- Breast tumor is HER-2 receptor negative, as determined by immunohistochemistry (IHC) or in situ hybridization (ISH) assay; **AND**
- Breast tumor size greater than 0.5 cm; **AND**
- Negative axillary lymph nodes (nonmetastatic) (pN0) or axillary-node micrometastasis (pN1mi) no greater than 2.0 mm; **AND**
- Individual has been assessed and determined to be a candidate for adjuvant chemotherapy (ie, chemotherapy is not disallowed due to other factors, such as advanced age or comorbidities); **AND**
- Prior to testing, physician has discussed possible test results with individual and agrees to use the results of the test for therapeutic management

Humana members may be eligible under the Plan for **58-gene assay (ie, Prosigna Breast Cancer Prognostic Gene Signature Assay [also known as PAM50 risk of recurrence score or PAM50])** for the management of breast cancer when the following criteria are met:

- Breast cancer newly diagnosed in a postmenopausal female; **AND**
- Breast tumor is estrogen-receptor (ER) positive; **AND**
- Breast tumor is HER-2 receptor negative, as determined by immunohistochemistry (IHC) or in situ hybridization (ISH) assay; **AND**

- Breast tumor size greater than 0.5 cm; **AND**

- Negative axillary lymph nodes (nonmetastatic) (pN0) or axillary-node micrometastasis (pN1mi) no greater than 2.0 mm; **AND**

- Individual has been assessed and determined to be a candidate for adjuvant chemotherapy (ie, chemotherapy is not disallowed due to other factors, such as advanced age or comorbidities); **AND**

- Prior to testing, physician has discussed possible test results with individual and agrees to use the results of the test for therapeutic management

**Multiple Primary Breast Tumors**

Humana members may be eligible under the Plan for **EndoPredict (EPclin), Oncotype DX Breast or Prosigna (PAM50) for the management of breast cancer for multiple primary breast tumors** when the following criteria are met:

- Each primary breast tumor must individually meet the criteria above for EndoPredict (EPclin), Oncotype DX Breast or Prosigna (PAM50); **AND**

- If each breast tumor meets criteria for testing, the Recurrence Score (RS) (ie, test result) from one tumor must be known before testing another tumor*****

*****If Recurrence Score (RS) on the first tumor is *high*, then testing on a subsequent tumor is unnecessary. If RS on the first tumor is *intermediate* or *low*, then testing on a subsequent tumor may be considered.

**Physician interpretation and reporting for molecular pathology procedures is considered integral to the primary molecular pathology procedure/laboratory testing and not separately reimbursable.**

*Coverage Limitations*

Humana members may **NOT** be eligible under the Plan for **gene expression profiling (GEP)** for any indications other than those listed above including, but may not be limited to:

- B-cell lymphoma classification including, but may not be limited to, primary mediastinal B-cell lymphoma, diffuse large B-cell lymphoma (ie, Lymph3Cx Lymphoma Molecular Subtyping Assay); **OR**
- Bladder cancer including, but may not be limited to:
  - 209-gene expression assay (ie, Decipher Bladder TURBT); **OR**
  - Genomic subtyping for management of locally advanced bladder cancer (ie, Decipher Bladder); **OR**
  - Urine-based cancer detection tests for biomarkers *MDK, HOXA13, CDC2 (CDK1), IGFBP5, CXCR2* for any indication including, but may not be limited to:
    - To identify urothelial carcinoma (ie, Cxbladder Detect); **OR**
    - To monitor recurrent urothelial carcinoma (ie, Cxbladder Monitor); **OR**
    - To rule out urothelial carcinoma (ie, Cxbladder Triage); **OR**
- Cancer of unknown primary (CUP) including, but may not be limited to:
  - 2000-gene expression assay (ie, Tissue of Origin [TOO], ResponseDX Tissue of Origin); **OR**
  - 92-gene expression assay (ie, CancerTYPE ID); **OR**
  - RosettaGX Cancer Origin; **OR**
- Colon cancer including, but may not be limited to:
  - 12-gene expression profile assay for colon cancer (ie, Oncotype DX for Colon); **OR**
  - 18-gene expression profile assay (ie, ColoPrint); **OR**

- Gene expression profiling of miR-31-3p for colorectal cancer (ie, miR-31now); **OR**
- GeneFx Colon Cancer Gene Signature; **OR**

- Gene expression by whole transcriptome sequencing (ie, OncoTarget/OncoTreat); **OR**

- Idiopathic pulmonary fibrosis including, but may not be limited to, 190-gene expression assay (ie, Envisia Genomic Classifier); **OR**

- Lung cancer including, but may not be limited to:
  - GeneFx Lung; **OR**
  - HistoPlus; **OR**
  - myPlan Lung Cancer test; **OR**
  - Percepta Bronchial Genomic Classifier; **OR**

- Management of breast cancer other than those listed above (ie, EndoPredict [EPclin], Oncotype DX Breast or Prosigna [PAM50]) including, but may not be limited to:
  - 11-gene assay for breast cancer (ie, Breast cancer index [BCI]); **OR**
  - 12-gene expression assay for ductal carcinoma in situ (DCIS) of the breast (ie, Oncotype DX DCIS Breast Cancer Test); **OR**
  - 70-gene panel assay (ie, MammaPrint); **OR**
  - 80-gene molecular subtyping assay (ie, BluePrint); **OR**
  - 100-gene panel assay to determine clinical subtypes for triple negative breast cancer (ie, Insight TNBC Type); **OR**
  - Breast cancer index (BCI); **OR**
  - ER, PR and HER2 status (eg, TargetPrint); **OR**

- Immunohistochemistry breast tumor tissue assay evaluating the following biomarkers: *CEACAM6, HYAL1, MMP-11, HEC1* (ie, BBDRisk Dx); **OR**

- Melanoma, cutaneous or uveal including, but may not be limited to:
  - 15-gene expression profiling assay for uveal melanoma (ie, DecisionDx-UM); **OR**
  - 31-gene expression profiling assay for cutaneous melanoma (ie, DecisionDx-Melanoma); **OR**
  - myPath Melanoma; **OR**
  - Pigmented Lesion Assay (PLA); **OR**
  - Uveal Melanoma Prognostic Test

These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **EndoPredict (EPclin), Oncotype DX or Prosigna (PAM50)** for the following indications:

- Node positive breast cancer; **OR**
- Repeat testing on the same breast tumor including with the use of a different gene expression profiling test

These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **Prosigna Breast Cancer Prognostic Gene Signature Assay (PAM50)** for any indications other than those listed above including, but may not be limited to, the following:

- Premenopausal female

This is considered experimental/investigational as it is not identified as widely used and generally accepted for any other proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

## Background

Additional information about **cancer and idiopathic pulmonary fibrosis** may be found from the following websites:

- American Cancer Society
- American Lung Association
- National Comprehensive Cancer Network
- National Library of Medicine
- Pulmonary Fibrosis Foundation

## Medical Alternatives

Alternatives to **GEP for cancer of unknown primary (CUP)** include, but may not be limited to:

- Biopsies and blood tests
- Imaging (eg, X-rays, ultrasound, computed tomography [CT] and magnetic resonance imaging [MRI])

Alternatives to **GEP for idiopathic pulmonary fibrosis** include, but may not be limited to:

- High resolution computed tomography (HRCT)
- Histopathologic analysis

Physician consultation is advised to make an informed decision based on an individual's health needs.

Humana may offer a disease management program for this condition. The member may call the number on his/her identification card to ask about our programs to help manage his/her care.

## Provider Claims Codes

Any CPT, HCPCS or ICD codes listed on this medical coverage 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 |
|---|---|---|
| 81287 | MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis | **Not Covered if used to report any test outlined in Coverage Limitations section** |
| 81401 | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) | **Not Covered if used to report any test outlined in Coverage Limitations section** |
| 81479 | Unlisted molecular pathology procedure | **Not Covered if used to report any test outlined in Coverage Limitations section** |
| 81493 | Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score | **Not Covered**<br><br>**Test Obsolete/No Longer Available** |
| 81504 | Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores | **Not Covered** |
| 81518 | Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy | **Not Covered** |
| 81519 | Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score | **Not Covered if used to report any test outlined in Coverage Limitations section** |

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| 81520 | Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score | |
| 81521 | Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis | **Not Covered** |
| 81522 | Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score | **Not Covered**<br><br>**New Code Effective 01/01/2020** |
| 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 | **Not Covered** |
| 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 | **Not Covered** |
| 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 | **Not Covered**<br><br>**New Code Effective 01/01/2020** |
| 81599 | Unlisted multianalyte assay with algorithmic analysis | **Not Covered if used to report any test outlined in Coverage Limitations section** |
| 84999 | Unlisted chemistry procedure | **Not Covered if used to report any test outlined in Coverage Limitations section** |

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| 88381 | Microdissection (ie, sample preparation of microscopically identified target); manual | |
| 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 | **Not Covered** |
| 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 | **Not Covered** |
| 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 | **Not Covered** |
| 0045U | Oncology (breast ductal carcinoma in situ), 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 recurrence score | **Not Covered** |
| 0057U | Oncology (solid organ neoplasia), mRNA, gene expression profiling by massively parallel sequencing for analysis of 51 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a normalized percentile rank | **Not Covered**<br><br>**Deleted Code Effective 06/30/2019** |
| 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 | **Not Covered** |
| 0069U | Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score | **Not Covered** |

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|---|---|---|
| 0081U | Oncology (uveal melanoma), mRNA, gene-expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping genes), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis | **Not Covered**<br><br>**Deleted Code Effective 12/31/2019** |
| 0089U | Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es) | **Not Covered**<br><br>**New Code Effective 07/01/2019** |
| 0090U | Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a categorical result (ie, benign, indeterminate, malignant) | **Not Covered**<br><br>**New Code Effective 07/01/2019** |
| 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 | **Not Covered**<br><br>**New Code Effective 10/01/2019** |
| 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 | **Not Covered**<br><br>**New Code Effective 01/01/2020** |
| **CPT® Category III Code(s)** | **Description** | **Comments** |
| No code(s) identified | | |
| **HCPCS Code(s)** | **Description** | **Comments** |

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|---|---|---|
| G0452 | Molecular pathology procedure; physician interpretation and report | **Considered integral to the primary molecular pathology procedure/laboratory testing and not separately reimbursable** |
| S3854 | Gene expression profiling panel for use in the management of breast cancer treatment | **Not Covered if used to report any test outlined in Coverage Limitations section** |

## Medical Terms

**Adjuvant** – Additional treatment used to increase the effectiveness of the primary therapy.

**Axillary** – Pertaining to the armpit area.

**Chemotherapy** – Use of chemicals or drugs to treat disease, usually in reference to cancer treatment.

**Cutaneous** – Of, relating to or affecting the skin.

**Deoxyribonucleic Acid (DNA)** – The molecule that carries genetic information in all living systems.

**Estrogen Receptor (ER)** – A hormone receptor test that determines if breast cancer cells have receptors for the hormone estrogen. Hormone receptors are proteins found in and on breast cells that pick up hormone signals telling the cells to grow.

**Genomic Subtyping** – Describes small groups that a type of cancer can be divided into, based on certain characteristics of the cancer cells.

**HER2 (Her2/neu, human epidermal growth factor receptor-2)** – A protein that appears in cancer cells, such as breast cancer. A tumor that has larger than normal levels of HER2 is considered HER2-positive while normal levels of HER2 are considered HER2-negative.

**High Resolution Computed Tomography (HRCT)** – A type of imaging (computed tomography [CT]) to detect various lung pathology.

**Histopathologic Analysis** – Microscopic examination of a biopsy or surgical specimen in order to study manifestations of disease.

**Idiopathic Pulmonary Fibrosis (IPF)** – A type of lung disease that results in scarring (fibrosis) of the lungs for an unknown reasons.

**Immunohistochemistry (IHC)** – Laboratory process of detecting an organism in tissues with antibodies.

**Locally Advanced Bladder Cancer** – Cancer that has spread through the bladder wall or has spread only to lymph nodes.

**Melanoma** – A malignant tumor associated with skin cancer.

**Microarray** – A laboratory technology to identify changes in genes or gene expression.

**Micrometastasis** – The spread of cancer cells from the primary site with the secondary tumors too small to be clinically detected.

**Nonmetastatic** – Cancer that has not spread from the primary or original site to other sites in the body.

**Progesterone Receptor (PR)** – A hormone receptor test that determines if breast cancer cells have receptors for the hormones progesterone. Hormone receptors are proteins found in and on breast cells that pick up hormone signals telling the cells to grow.

**Prognosis** – A forecast of the likely course of a disease or ailment.

**Ribonucleic Acid (RNA)** – A long, single-stranded chain of cells that processes protein.

**Uveal** – Of, relating to, affecting or being the uvea, the middle layer of the eye consisting of the iris and ciliary body together with the choroid coat.

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