Gene Expression Profiling

Medical Coverage Policy

Effective Date: 08/22/2013
Revision Date: 08/22/2013
Review Date: 07/25/2013
Policy Number: CLPD-0458-018

Change Summary: Updated Coverage Limitations

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<table>
<thead>
<tr>
<th>Disclaimer</th>
<th>Medical Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Provider Claims Codes</td>
</tr>
<tr>
<td>Coverage Determination</td>
<td>Medical Terms</td>
</tr>
<tr>
<td>Background</td>
<td>References</td>
</tr>
</tbody>
</table>

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Description

Gene expression profiling (GEP) is a method of laboratory testing that measures messenger ribonucleic acid (RNA) expressed from various genes in many different cell types. This testing allows specially trained professionals to examine genetic end products, such as proteins and metabolites, in an attempt to determine the effects treatments have on individual gene expressions.

GEP has been primarily studied and used clinically to determine prognosis, refine risk stratification and/or optimize treatment regimens for cancer, most notably, breast (e.g., Oncotype DX®, MammaPrint®). More recently, GEP has been used to assess thyroid nodules (e.g., Afirma® Thyroid FNA Analysis). Other proposed cancer indications include, but may not be limited to: colon, glioblastoma, lung, lymphoma, melanoma, myeloma, prostate, unknown primary and uveal melanoma. (Refer to Coverage Limitations section)
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Review Date: 07/25/2013
Policy Number: CLPD-0458-018
Page: 2 of 31

GEP has also been proposed for use for noncancer indications, such as coronary artery disease (CAD) (e.g., Corus™ CAD). (Refer to Coverage Limitations section)

DNA Specimen Provenance Assignment (DSPA) Testing (e.g., Know Error® System) is a molecular diagnostic test intended for the protection and control of tissue samples to purportedly decrease the incidence of diagnostic mistakes due to patient misidentification, specimen transposition or cell contamination, known as specimen provenance complications (SPCs). Breast and prostate tissues are most often tested but other tissue types may also be examined including, but not limited to, bone marrow biopsies.

Coverage Determination

Breast Cancer

Humana members may be eligible under the Plan for Oncotype DX® gene expression assay for predicting breast cancer recurrence when the following criteria are met:

- Newly diagnosed breast cancer; AND
- Stage I or II breast cancer; AND
- Breast tumor is estrogen-receptor (ER) positive; AND
- Breast tumor is HER-2 receptor negative, as determined by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH); AND
- Tumor size greater than 0.5 cm; AND
- Negative axillary lymph nodes (nonmetastatic) (pN0); AND
- Patient is a candidate for adjuvant chemotherapy (i.e., chemotherapy is not disallowed due to other factors, such as advanced age or comorbidities)

Humana members may be eligible under the Plan for MammaPrint® gene expression assay for predicting breast cancer recurrence when the following criteria are met:

- Newly diagnosed breast cancer; AND

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- Stage I or II breast cancer; **AND**
- Estrogen-receptor (ER) positive or ER negative; **AND**
- Tumor size less than or equal to 5.0 cm; **AND**
- Negative axillary lymph nodes (nonmetastatic) defined as:
  - Standard axillary lymph node dissection negative by hematoxylin and eosin (H&E) staining; **OR**
  - Sentinel lymph node negative by H&E staining, even if immunoassay positive; **AND**
- Patient is a candidate for adjuvant chemotherapy (i.e., chemotherapy is not disallowed due to other factors, such as advanced age or comorbidities)

**Multiple Primary Breast Tumors**

Humana members may be eligible under the Plan for **Oncotype DX® gene expression assay** or **MammaPrint® gene expression assay** for predicting breast cancer recurrence for multiple primary breast tumors when the following criteria are met:

- Each primary breast tumor MUST separately meet the criteria above for Oncotype DX or MammaPrint for predicting breast cancer recurrence; **AND**
- If both breast tumors meet criteria for testing, the Recurrence Score (RS) (i.e., test results) from one tumor must be known before testing another tumor*

*Note: 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.

**Thyroid Nodules**

Humana members may be eligible under the Plan for **Afirma® Thyroid FNA Analysis** to assess thyroid nodules following indeterminate fine needle aspiration (FNA) cytology.
Laboratory quality control, including DNA Specimen Provenance Assignment (DSPA) testing to decrease specimen provenance complications (SPC), (e.g., Know Error® System), is considered integral to the primary procedure and not separately reimbursable.

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** for any indication other than those listed above including, but not limited to, the following:

- Cancer of unknown primary (CUP) (e.g., CancerTYPE ID®, PathWork Tissue of Origin, miRview® mets², ProOnc TumorSource DX™); **OR**
- Colon cancer (e.g., Oncotype DX® Colon, ColoPrint®, GeneFx® Colon); **OR**
- Coronary artery disease (CAD) (e.g., Corus™ CAD)
- Diffuse large B-cell lymphoma (e.g., ENGAUGE™-cancer-DLBCL); **OR**
- ER, PR and HER2 status (e.g., TargetPrint®); **OR**
- Glioblastoma multiforme (e.g., MGMT promoter methylation, DecisionDx-GBM); **OR**
- Lung cancer (e.g., GeneFx® Lung); **OR**
- Melanoma (e.g., DecisionDx-Melanoma); **OR**
- Myeloma (e.g., MyPRS Plus™); **OR**
- Prostate cancer (e.g., ConfirmMDx™ for Prostate Cancer, Oncotype DX® Prostate, PCA3, Prolaris®, Proveri Prostate Cancer Assay [PPCA™]); **OR**
- Uveal melanoma (e.g., DecisionDx-UM)

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

Humana members may NOT be eligible under the Plan for **gene expression assays for predicting breast cancer recurrence other than Oncotype DX® or MammaPrint®** including, but not limited to, the following:

- Breast Cancer Gene Expression Profile (BreastOncPx™); OR
- Clariant Insight® Dx Breast Cancer Profile; OR
- H/I™ (HOXB13:IL17BR) Gene Expression Ratio; OR
- Mammastatin; OR
- Mammastrat®; OR
- Rotterdam Signature

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

Humana members may NOT be eligible under the Plan for **Oncotype DX®** for any of the following:

- Micrometastatic breast cancer; OR
- Node positive breast cancer; OR
- Oncotype DX® DCIS for ductal carcinoma in situ (DCIS) of the breast

This technology is considered experimental/investigational as it is 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 **repeat gene expression profiling for breast cancer on the same breast tumor**, including Oncotype DX® Breast following previous MammaPrint® testing or MammaPrint® following previous Oncotype DX® Breast testing.

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This technology is considered experimental/investigational as it is 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 repeat Afirma® Thyroid FNA Analysis for the assessment of thyroid nodules. This technology is considered experimental/investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may NOT be eligible under the Plan for self-testing home kits due to potential risks associated with genetic testing such as inappropriate testing, misinterpretation of results, inaccurate or not clinically valid testing, lack of follow-up care and other adverse consequences.

Background

Additional information about cancer and coronary artery disease may be found from the following websites:

- American Cancer Society - [http://www.cancer.org](http://www.cancer.org)
- American Heart Association - [http://www.heart.org/HEARTORG/](http://www.heart.org/HEARTORG/)

Medical Alternatives

Alternatives to gene expression profiling for CAD include, but may not be limited to, the following:

- Traditional risk factor analysis, including cholesterol (please refer to Cardiovascular (CVD) Risk Testing - Laboratory Medical Coverage Policy)

Alternatives to gene expression profiling for cancer of unknown primary (CUP) include, but may not be limited to, the following:

- Biopsies and blood tests
- Imaging, such as X-rays, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI)
To make the best health decision for the patient’s individual needs, the patient should consult his/her physician.

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

Provider Claims Codes

All provider claims codes surrounding this topic may not be included in the following table:

<table>
<thead>
<tr>
<th>CPT® Code(s)</th>
<th>Description</th>
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</tr>
</thead>
<tbody>
<tr>
<td>81265</td>
<td>Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)</td>
<td><strong>No separate reimbursement if used to report laboratory quality control, including DNA Specimen Provenance Assignment (DSPA) testing to decrease specimen provenance complications (SPC), such as Know Error® System</strong></td>
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<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
<td><strong>Not Covered if used to report genetic testing outlined in the Coverage Limitations section of this Medical Coverage Policy</strong></td>
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New Code Effective 01/01/2013
### Gene Expression Profiling

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**Revision Date:** 08/22/2013  
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**Policy Number:** CLPD-0458-018

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<td>83890</td>
<td>Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)</td>
<td>Not Covered if used to report genetic testing outlined in the Coverage Limitations section of this Medical Coverage Policy</td>
<td>12/31/2012</td>
</tr>
<tr>
<td>83891</td>
<td>Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)</td>
<td>Not Covered if used to report genetic testing outlined in the Coverage Limitations section of this Medical Coverage Policy</td>
<td>12/31/2012</td>
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<tr>
<td>83892</td>
<td>Molecular diagnostics; enzymatic digestion, each enzyme treatment</td>
<td>Not Covered if used to report genetic testing outlined in the Coverage Limitations section of this Medical Coverage Policy</td>
<td>12/31/2012</td>
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</tbody>
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</tr>
</thead>
<tbody>
<tr>
<td>83893</td>
<td>Molecular diagnostics; dot-slot blot production, each nucleic acid preparation</td>
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<td>12/31/2012</td>
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<tr>
<td>83894</td>
<td>Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation</td>
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<tr>
<td>83896</td>
<td>Molecular diagnostics; nucleic acid probe, each</td>
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</tbody>
</table>
Gene Expression Profiling
Effective Date: 08/22/2013
Revision Date: 08/22/2013
Review Date: 07/25/2013
Policy Number: CLPD-0458-018
Page: 10 of 31

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<tbody>
<tr>
<td>83897</td>
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<tr>
<td>83898</td>
<td>Molecular diagnostics; amplification, target, each nucleic acid sequence</td>
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<td>83900</td>
<td>Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences</td>
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<td>12/31/2012</td>
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<tr>
<td>83901</td>
<td>Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)</td>
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<tr>
<td>83902</td>
<td>Molecular diagnostics; reverse transcription</td>
<td>Not Covered if used to report genetic testing outlined in the Coverage Limitations section of this Medical Coverage Policy</td>
</tr>
</tbody>
</table>
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<tr>
<td>83904</td>
<td>Molecular diagnostics; mutation identification by sequencing, single segment, each segment</td>
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<tr>
<td>83905</td>
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<td>83906</td>
<td>Molecular diagnostics; mutation identification by allele specific translation, single segment, each segment</td>
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<tr>
<td>83907</td>
<td>Molecular diagnostics; lysis of cells prior to nucleic acid extraction (eg, stool specimens, paraffin embedded tissue), each specimen</td>
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<td>83908</td>
<td>Molecular diagnostics; amplification, signal, each nucleic acid sequence</td>
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<td>83909</td>
<td>Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation</td>
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<td>83912</td>
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<td>83913</td>
<td>Molecular diagnostics; RNA stabilization</td>
<td>Not Covered if used to report genetic testing outlined in the Coverage Limitations section of this Medical Coverage Policy</td>
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<td>83914</td>
<td>Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay [OLA], single base chain extension [SBCE], or allele-specific primer extension [ASPE])</td>
<td>Not Covered if used to report genetic testing outlined in the Coverage Limitations section of this Medical Coverage Policy</td>
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<td>84999</td>
<td>Unlisted chemistry procedure</td>
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<td>88360</td>
<td>Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, each antibody; manual</td>
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<tr>
<td>88384</td>
<td>Array-based evaluation of multiple molecular probes; 11 through 50 probes</td>
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<td>Not Covered if used to report genetic testing outlined in the Coverage Limitations section of this Medical Coverage Policy</td>
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<td>88386</td>
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<td>Deleted Code Effective 12/31/2012</td>
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<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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**CPT® Category III Code(s)**

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**HCPCS Code(s)**

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<tr>
<td>Molecular pathology procedure; physician interpretation and report</td>
<td>Considered integral to the primary molecular pathology procedure/laboratory testing and not separately reimbursable</td>
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<td>ICD-9 Procedure Code(s)</td>
<td>Description</td>
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<td>------------------------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes</td>
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<tr>
<td>S3721</td>
<td>Prostate cancer antigen 3 (PCA3) testing</td>
</tr>
<tr>
<td>S3854</td>
<td>Gene expression profiling panel for use in the management of breast cancer treatment</td>
</tr>
</tbody>
</table>

### 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.
- **Deoxyribonucleic Acid (DNA)** - The molecule that carries genetic information in all living systems.
- **Estrogen Receptor (ER)** - Measure of the degree to which a tumor is dependent upon estrogen for its growth. It is often written as ER+ (the tumor is positive for dependence upon estrogen) or ER- (the tumor is negative for dependence upon estrogen).
- **Fluorescence in Situ Hybridization (FISH)** - Laboratory technique used to detect small deletions or rearrangements in chromosomes.
- **Glioblastoma Multiforme** - The most common and most aggressive of brain tumors.
- **Hematoxylin & Eosin (H&E) Staining** - Stain routinely used to examine substances.
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.

Immunostain - Laboratory technique used to identify substances in blood or tissue; based on the use of antibodies.

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

Lymph Node Dissection - Surgical procedure in which the lymph nodes are removed and examined to determine if cancer is present.

Mammastatin - Human protein found in blood, but absent or at lower levels in breast cancer patients.

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.

Polymerase Chain Reaction (PCR) - Laboratory process to detect small amounts of DNA or RNA in blood or tissue.

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

Uveal Melanoma - Malignant melanoma arising from the structures of the eye.

References


Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program


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Policy Number: CLPD-0458-018
Page: 21 of 31


Gevensleben H, Göhring U, Büttner R, et al. Comparison of MammaPrint and TargetPrint results with clinical parameters in German patients with early stage breast...


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National Cancer Institute (NCI) Website. Intraocular (uveal) melanoma treatment
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UpToDate® Website. Hormone receptors in breast cancer: clinical utility and guideline recommendations to improve test accuracy. June 2013. Available at:
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Gene Expression Profiling

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Page: 30 of 31

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