of Tennessee

Policy

# Reimbursement Policy

## Serum Tumor Markers for Malignancies



### I. Policy Description

Circulating tumor biomarkers are substances detected in the blood, urine, or other body fluids that are either produced by a tumor itself or in response to its presence. These biomarkers can be used to help detect, diagnose, stage, and manage some types of cancer, because their amounts are typically elevated in individuals harboring a tumor.[1,2] There are currently dozens of tumor markers in common use; this laboratory policy addresses tumor markers which may be measured in an individual's serum.

Terms such as male and female are used when necessary to refer to sex assigned at birth.

The following management of serum tumor markers is built from recommendations from the National Comprehensive Cancer Network (NCCN) Biomarkers Compendium®, which contains information "designed to support decision making around the use of biomarker testing in patients with cancer. The NCCN Biomarkers Compendium® is updated in conjunction with the NCCN Guidelines on a continual basis."[3]

### II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

*Note: Except for where otherwise specified in the coverage criteria below, quarterly measurement of designated serum biomarkers is permitted for follow-up, monitoring, and/or surveillance*

1) Measurement of the following serum biomarkers **MEETS COVERAGE CRITERIA** for the following indications:

| Serum Biomarker | Indication |
|---|---|
| **Alkaline phosphatase (ALP)** | Bone neoplasms: **workup**<br>Melanoma (uveal): **workup** |

# Reimbursement Policy

| Serum Biomarker | Indication |
|---|---|
| | Systemic light chain amyloidosis: **initial diagnostic workup** |
| **Alpha fetoprotein (AFP)** | Hepatocellular carcinoma: **screening**; **workup** for confirmed HCC; **surveillance** (every 3-6 months for 2 years, then every 6 months) |
| | Intrahepatic cholangiocarcinoma: **workup** for isolated intrahepatic mass |
| | Occult primary: **additional workup** for localized adenocarcinoma or carcinoma not otherwise specified; liver, mediastinum, or retroperitoneal mass |
| | Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated) |
| | Ovarian cancers (less common):<br>– Carcinosarcoma (malignant mixed mullerian tumors): **monitoring/follow-up**<br>– Clear cell carcinoma of the ovary: **monitoring/follow-up**<br>– Grade 1 endometrioid carcinoma: **monitoring/follow-up**<br>– Mucinous neoplasms of the ovary: **monitoring/follow-up**<br>– Low-grade serous carcinoma: **monitoring/follow-up**<br>Ovarian cancers:<br>– Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated)<br>– Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5)<br>– Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) |
| | Testicular cancer – nonseminoma: **workup**; **risk classification**; **surveillance** (no more than every 2 months) |
| | Testicular cancer - pure seminoma: **initial diagnostic workup**; **post-diagnostic workup**; **risk classification**; **post-treatment surveillance** (no more than every 2 months) |
| | Thymomas and thymic carcinomas: **initial evaluation**, if appropriate |
| **Beta-2 microglobulin (B2M)** | B-cell lymphomas (diffuse large B-cell; follicular [grade 1-2]; HIV-related; lymphoblastic; mantle cell): **workup** |
| | Castleman Disease: workup |

| Serum Biomarker | Indication |
|---|---|
| | Chronic lymphocytic leukemia/small lymphocytic lymphoma: **workup**; for **prognostic** and/or **therapy determination** |
| | Multiple myeloma: **initial diagnostic workup**; **follow-up/surveillance** (as needed) for solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement |
| | Systemic light chain amyloidosis: **initial diagnostic workup** |
| | Waldenström macroglobulinemia / lymphoplasmacytic lymphoma: **workup** |
| **BNP or NT-proBNP** | Multiple myeloma: **initial diagnostic workup** |
| **Calcitonin (CALCA)** | Adenocarcinoma, and anaplastic/undifferentiated epithelial tumors: **workup** |
| | Medullary carcinoma: **additional workup**; **post-surgical evaluation**; **monitoring**; **surveillance** (2-3 months postoperative, then every 6-12 months) |
| | Multiple endocrine neoplasia, type 2: **at diagnosis** (clinical evaluation) for medullary thyroid cancer |
| | Occult primary (unknown primary cancer): **workup** |
| **Cancer antigen 15-3 and 27.29 (CA 15-3 and 27.29)** | Breast cancer (invasive): **monitoring** metastatic disease |
| | Occult primary: suspected metastatic malignancy: **initial workup**; assessing disease **prognosis**; **monitoring/follow-up** for response |
| **Cancer antigen 19-9 (CA 19-9)** | Ampullary adenocarcinoma: **workup**; **surveillance** (every 3-6 months for 2 years, then every 6-12 months for up to 5 years as clinically indicated) for resected ampullary cancer, stage I-III |
| | Appendiceal adenocarcinoma: **workup** to establish baseline. Abnormal measurements should be trended |
| | Extrahepatic cholangiocarcinoma: **workup** to establish baseline; **monitoring** |
| | Gallbladder cancer: **workup** to establish baseline; **monitoring**; **surveillance** (as clinically indicated), post-resection |
| | Intrahepatic cholangiocarcinoma: **workup** to establish baseline; **monitoring** |
| | Occult primary: workup to establish baseline; |
| | Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated) |

# Reimbursement Policy

| Serum Biomarker | Indication |
|---|---|
| | Ovarian cancers (less common):<br>– Carcinosarcoma (malignant mixed mullerian tumors): **workup/monitoring/follow up**<br>– Clear cell carcinoma of the ovary: **workup/monitoring/follow up**<br>– Grade 1 endometrioid carcinoma: **workup/monitoring/follow up**<br>– Low-grade serous carcinoma: **workup/monitoring/follow up**<br>– Mucinous neoplasms of the ovary: **workup/monitoring/follow up**<br>Ovarian cancers<br>– Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated)<br>– Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5)<br>– Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)<br>– Mucinous carcinoma of the ovary: **additional workup** (if not previously done) |
| | Pancreatic adenocarcinoma: **workup** to establish baseline; **monitoring**; **post-operative**, **post-adjuvant treatment surveillance** (every 3-6 months for 2 years, then every 6-12 months as clinically indicated) |
| | Small bowel adenocarcinoma: **workup** to establish baseline; **post-treatment surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years); **at metastasis or recurrence** |
| **Cancer antigen 125 (CA-125)** | Appendiceal adenocarcinoma: **workup** to establish baseline |
| | Endometrial carcinoma: **additional workup**; **surveillance** (if initially elevated) |
| | Lynch syndrome: **surveillance** |
| | Occult primary: initial evaluation/workup, **additional workup** for adenocarcinoma or carcinoma not otherwise specified, in those with a uterus and/or ovaries present |
| | Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated) |

| Serum Biomarker | Indication |
|---|---|
| | Ovarian cancers (less common):<br>– Carcinosarcoma (malignant mixed mullerian tumors): **monitoring/follow-up**<br>– Clear cell carcinoma of the ovary: **monitoring/follow-up**<br>– Mucious neoplasms of the ovary: **monitoring/follow-up**<br>– Grade 1 endometrioid carcinoma: **monitoring/follow-up**<br>– Low-grade serous carcinoma: **monitoring/follow-up**<br>Ovarian cancers:<br>– Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated)<br>– Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 6 months in years 3-5, and then annually after year 5)<br>– Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) |
| | Peritoneal mesothelioma: **initial evaluation** |
| | Uterine neoplasms: **initial workup, additional workup, surveillance** |
| **Carcinoembryonic antigen (CEA)** | Appendiceal adenocarcinoma: **workup** to establish baseline; **monitoring**; **post-treatment surveillance** |
| | Breast cancer (invasive): **Monitoring** metastatic disease |
| | Colon cancer: **workup** to establish baseline; **monitoring**; **surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years) |
| | Extrahepatic cholangiocarcinoma: **workup** to establish baseline; **monitoring** |
| | Gallbladder cancer: **workup** to establish baseline; **monitoring**; **surveillance; monitoring of adjuvant treatment** (as clinically indicated), **post-resection** |
| | Intrahepatic cholangiocarcinoma: **workup** to establish baseline; **monitoring** |
| | Medullary carcinoma: **diagnosis and additional workup**; **monitoring**; **post-surgical surveillance** (2-3 months postoperative, then every 6-12 months) |
| | Multiple endocrine neoplasia, type 2: **at diagnosis** (clinical evaluation) for medullary thyroid cancer |
| | Occult primary (unknown primary cancer): **workup** for adenocarcinoma or carcinoma not otherwise specified |

| Serum Biomarker | Indication |
|---|---|
| | Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated) |
| | Ovarian cancers (less common):<br>– Carcinosarcoma (malignant mixed mullerian tumors: **monitoring/follow-up**<br>– Clear cell carcinoma of the ovary: **monitoring/follow-up**<br>– Grade 1 endometrioid carcinoma: **monitoring/follow-up**<br>– Low-grade serous carcinoma: **monitoring/follow-up**<br>– Mucinous neoplasms of the ovary: **monitoring/follow-up**<br>Ovarian cancers:<br>– Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated); **post-adjuvant treatment**<br>– Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5)<br>– Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)<br>– Mucinous carcinoma of the ovary: **additional workup** (if not previously done) |
| | Rectal cancer: **workup** to establish baseline; **monitoring**; **surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years) |
| | Small bowel adenocarcinoma: **workup** to establish baseline; **post-treatment surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years) |
| **Chorionic gonadotropin beta polypeptide (CGB3)** | Gestational trophoblastic neoplasia: **initial workup**; **during and post treatment** (no more than weekly); **follow-up/surveillance** (no more than monthly for 12 months) |
| | Occult primary: **additional workup** for localized adenocarcinoma or carcinoma not otherwise specified; individuals < 65 years of age with mediastinum or retroperitoneal mass |
| | Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated) |
| | Ovarian cancers: |

| Serum Biomarker | Indication |
|---|---|
| | – Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated)<br>– Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5)<br>– Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) |
| | Testicular cancer – nonseminoma: **workup; risk classification; surveillance** (no more than every 2 months) |
| | Testicular cancer – pure seminoma: **workup; post-diagnostic workup; risk classification; post-treatment surveillance** (no more than every 2 months) |
| | Thymomas and thymic carcinomas: **initial evaluation**, if appropriate |
| **Human epididymis protein 4 (HE4)** | Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated) |
| | Ovarian cancers (less common):<br>– Carcinosarcoma (malignant mixed mullerian tumors: **monitoring/follow-up**<br>– Clear cell carcinoma of the ovary: **monitoring/follow-up**<br>– Grade 1 endometrioid carcinoma: **monitoring/follow-up**<br>– Low-grade serous carcinoma: **monitoring/follow-up**<br>– Mucinous neoplasms of the ovary: **monitoring/follow-up**<br>Ovarian cancers :<br>– Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated); **post-adjuvant treatment**<br>– Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5)<br>– Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) |
| **Inhibin (INHA)** | Occult primary (unknown primary cancer): **additional workup** for adenocarcinoma or carcinoma not otherwise specified |

# Reimbursement Policy

| Serum Biomarker | Indication |
|---|---|
| | Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated) |
| | Ovarian cancers (less common):<br>– Carcinosarcoma (malignant mixed mullerian tumors: **monitoring/follow-up**<br>– Clear cell carcinoma of the ovary: **monitoring/follow-up**<br>– Grade 1 endometrioid carcinoma: **monitoring/follow-up**<br>– Low-grade serous carcinoma: **monitoring/follow-up**<br>– Mucinous neoplasms of the ovary: **monitoring/follow-up**<br>Ovarian cancers:<br>– Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated)<br>– Malignant Germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5)<br>– Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) |
| **Serum free light chains** | Castleman disease: workup |
| | Multiple myeloma: **initial diagnostic workup**; **follow-up; surveillance** (up to once per month) |
| | Systemic light chain amyloidosis: **initial diagnostic workup** |
| **Troponin T** | Systemic light chain amyloidosis: **initial diagnostic workup** |
| **Tryptase** | Systemic mastocytosis: **initial diagnosis** |

*The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.*

2) For all other cancer indications not discussed above, use of the above biomarkers (alone or in a panel of serum tumor markers) **DOES NOT MEET COVERAGE CRITERIA.**

3) All other serum tumor markers not addressed above (alone or in a panel of serum tumor markers) **DO NOT MEET COVERAGE CRITERIA.**

4) For the screening and detection of cancer, analysis of proteomic patterns in serum **DOES NOT MEET COVERAGE CRITERIA**.

## III. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

**Food and Drug Administration (FDA)**

There are numerous FDA-approved tests for the assessment of serum tumor markers. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid Services (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

## IV. Applicable CPT/HCPCS Procedure Codes

| CPT | Code Description |
|---|---|
| 81479 | Unlisted molecular pathology procedure |
| 81599 | Unlisted multianalyte assay with algorithmic analysis |
| 82105 | Alpha-fetoprotein (AFP); serum |
| 82107 | Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP (including ratio) |
| 82232 | Beta-2 microglobulin |
| 82308 | Calcitonin |
| 82378 | Carcinoembryonic antigen (CEA) |
| 83520 | Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified |

# Reimbursement Policy

| CPT | Code Description |
|---|---|
| 83521 | Immunoglobulin light chains (ie, kappa, lambda), free, each |
| 83789 | Mass spectrometry and tandem mass spectrometry (eg, MS, MS/MS, MALDI, MS-TOF, QTOF), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen |
| 83880 | Natriuretic peptide |
| 83950 | Oncoprotein; HER-2/neu |
| 83951 | Oncoprotein; des-gamma-carboxy-prothrombin (DCP) |
| 84075 | Phosphatase, alkaline |
| 84078 | Phosphatase, alkaline; heat stable (total not included) |
| 84080 | Phosphatase, alkaline; isoenzymes |
| 84484 | Troponin, quantitative |
| 84702 | Gonadotropin, chorionic (hCG); quantitative |
| 84703 | Gonadotropin, chorionic (hCG); qualitative |
| 84704 | Gonadotropin, chorionic (hCG); free beta chain |
| 84999 | Unlisted chemistry procedure |
| 86300 | Immunoassay for tumor antigen, quantitative; CA 15-3 (27.29) |
| 86301 | Immunoassay for tumor antigen, quantitative; CA 19-9 |
| 86304 | Immunoassay for tumor antigen, quantitative; CA 125 |
| 86305 | Human epididymis protein 4 (HE4) |
| 86316 | Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), |
| 86336 | Inhibin A |
| 0404U | Oncology (breast), semiquantitative measurement of thymidine kinase activity by immunoassay, serum, results reported as risk of disease progression<br>Proprietary test: Divitum®Tka<br>Lab/Manufacturer: Biovica Inc |
| 0558U | Oncology (colorectal), quantitative enzyme-linked immunosorbent assay (ELISA) for secreted colorectal cancer protein marker (BF7 antigen), using serum, result reported as indicative of response/no response to therapy or disease progression/regression<br>Proprietary test: IGoCheckTM (Blood-Based Colorectal Cancer Test)<br>Lab/Manufacturer: Milagen, Inc |
| 0559U | Oncology (breast), quantitative enzyme-linked immunosorbent assay (ELISA) for secreted breast cancer protein marker (BF9 antigen), serum, result reported as indicative of response/no response to therapy or disease progression/regression<br>Proprietary test: Haystack MRDTM Baseline<br>Lab/Manufacturer: Quest Diagnostics® |

*Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.*

## V. Evidence-based Scientific References

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## VI. Revision History

| Revision Date | Summary of Changes |
|---|---|
| 06/04/2025 | Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Based on guidance from the National Comprehensive Cancer Network's Biomarker's Compendium, the following coverage additions and removals were made:<br><br>Adjusted terminology from 'serum tumor markers' in Note and CC1 to broaden definition as some serum-related markers are more accurately described as biomarkers rather than serum tumor markers. Changed title in table from "Serum Tumor Markers" to "Serum Biomarkers."<br><br>**Alkaline phosphatase:** For ALP, removed "during treatment, surveillance" from indications for ALP testing for bone neoplasms. Added "Melanoma (uveal)" as an indication for workup for ALP. Removed the words "post-diagnostic" from "Testicular cancer – nonseminoma" to clarify that workup can occur before or after diagnosis.<br><br>**Beta-2 microglobulin:** For Beta-2 microglobulin, removed "Castleman disease" from B-cell lymphoma title and created a new row which identifies the indication for Castleman disease as "workup" with B2M measurement.<br><br>**Chorionic gonadotropin beta polypeptide expression (CGB3):** Changed the title of "Beta-human chorionic gonadotropin (beta-HCG)" to "Chorionic gonadotropin beta polypeptide (CGB3)." Changed the words "testes presenting with" to "mediastinum or" under "Occult primary" designation.<br><br>**BNP or NT-proBNP:** For BNP or NT-proBNP, removed "systemic light chain amyloidosis" and indication for "initial diagnostic workup" from BNP or NT-proBNP section (this was moved to a separate section with Troponin T.).<br><br>**Cancer antigen 19-9 (CA 19-9):** For cancer antigen 19-9 (CA 19-9), removed "assessing disease prognosis; monitoring/follow-up for response" from Occult primary indications. In "Ovarian cancers (less common)" merged ovarian cancer sections. Added "monitoring/follow up" as indications to "Carcinosarcoma, |

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| | Clear cell carcinoma of the ovary, Grade 1 endometrial carcinoma, low-grade serous carcinoma," and "mucinous neoplasms of the ovary."<br><br>**Cancer antigen 125 (CA-125**): For cancer antigen 125 (CA-125), added "initial evaluation/workup" to indications for Occult primary. Added "additional workup/surveillance" indications to uterine neoplasms.<br><br>**Carcinoembryonic antigen (CEA):** For Carcinoembryonic antigen (CEA), added Occult primary and indication for "workup for adenocarcinoma or carcinoma not otherwise specified."<br><br>**Human epididymis protein 4 (HE4):** For Human epididymis protein 4, added new section to the table. Added "Ovarian cancer/fallopian tube cancer/primary peritoneal cancer" with indications for "initial workup during primary chemotherapy; monitoring/follow-up for complete response (as clinically indicated)." Added "Ovarian cancers (less common) and indications for various cancers under this designation for "monitoring/follow-up." Added "Ovarian cancers" and additional indications for "borderline epithelial tumors, malignant germ cell tumors, malignant sex cord stromal tumors."<br><br>**Inhibin (INHA):** For Inhibin (INHA), removed "adrenocortical carcinoma" and indication for "workup" from Inhibin (INHA) section. Added "Occult primary (unknown primary cancer)" with indications for "additional workup for adenocarcinoma or carcinoma not otherwise specified."<br><br>**Lactate dehydrogenase (LDH):** Removed the entire section on Lactate dehydrogenase (LDH) as LDH is a broad marker beyond serum tumor biomarker designation.<br><br>**Serum free light chains:** Under Serum free light chains added "Castleman disease:" with indications for "workup" and added "follow-up" to Multiple myeloma as an indication.<br><br>Added CPT code 0558U, 0559U (effective date 7/1/2025)<br><br>Removed CPT code 83615 |

# Reimbursement Policy