BSC_CON_2.11	Oncology: Cytogenetic Testing		
Original Policy Date:	December 1, 2023	**Effective Date:**	July 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 25

Example Test Table

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests	*ALK* Gene Rearrangements (Labcorp)	88271, 88274
Bladder Cancer Diagnostic and Recurrence FISH Tests	UroVysion FISH (ARUP Laboratories)	88120, 88121
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis	FISH for Chronic Lymphocytic Leukemia (Cleveland Clinic Laboratories)	88271, 88274, 88275, 88291
	FISH, B-Cell Chronic Lymphocytic Leukemia Panel (Quest Diagnostics)	
Tumor Specific *ERBB2* (*HER2*) Deletion/Duplication (FISH and CISH)	ERBB2 (HER2/neu) Gene Amplification by FISH with Reflex, Tissue (ARUP Laboratories)	88360, 88377
Multiple Myeloma FISH Panel Analysis	Oncology FISH Analysis - Multiple Myeloma FISH Panel (Baylor Genetics, LLC)	88271, 88237, 88275, 88291
	Multiple Myeloma (MM) FISH Profile (Labcorp)	
NTRK Fusion Analysis Panel	NTRK NGS Fusion Panel (NeoGenomics Laboratories)	81191, 81192, 81193, 81194
Tumor Specific *PD-L1* Protein Analysis	PD-L1, IHC with Interpretation (Quest Diagnostics)	88341, 88342, 88360, 88361
Tumor Specific FOLR1 Protein Analysis	FOLR1 Immunohistochemistry Analysis (Labcorp)	88360
Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR)	FISH, AML M3, PML/RARA, Translocation 15, 17 (Quest Diagnostics)	81315, 81316, 88271, 88274, 88275, 88291
	PML/RARA t(15;17) (NeoGenomics Laboratories))	
Tumor Specific *RET* Gene 0Rearrangement (FISH)	RET FISH (NeoGenomics Laboratories)	88374, 88377, 88271, 88275, 88291
	Oncology FISH Analysis - RET Rearrangement (Baylor Genetics)	
Tumor Specific *ROS1* Gene Rearrangement	FISH ROS1 Rearrangement (Johns Hopkins Medical Institutions-Pathology Laboratory)	88271, 88274

Policy Statement

Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests

I. Somatic *ALK* rearrangement analysis (88271, 88274) in solid tumors is considered **medically necessary** when:
   A. The member has a diagnosis of or is in the initial work up stage for **any** of the following:
      1. Stage IB or higher lung adenocarcinoma
      2. Stage IB or higher large cell lung carcinoma
      3. Stage IB or higher squamous cell lung carcinoma
      4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS)
      5. Anaplastic thyroid carcinoma
      6. Locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma
      7. Locally recurrent, advanced, and/or metastatic follicular thyroid cancer
      8. Locally advanced/metastatic ampullary adenocarcinoma
      9. Langerhans cell histiocytosis
      10. Erdheim-Chester disease
      11. Resectable, borderline resectable or locally advanced or metastatic pancreatic adenocarcinoma
      12. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma.

Bladder Cancer Diagnostic and Recurrence FISH Tests

II. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for diagnosing, and monitoring bladder cancer may be considered **medically necessary** when:
   A. The member meets **one** of the following:
      1. The member has hematuria, **AND both** of the following:
         a. Diagnostic studies have failed to identify the etiology of the hematuria
         b. A bladder cancer diagnostic and recurrence FISH test has not been ordered more than 1 time in the past 12 months, **OR**
      2. The member has been treated for bladder cancer, **AND**
         a. The bladder cancer diagnostic and recurrence FISH tests are ordered with **any** of the following frequency:
            i. No more than 4 bladder tumor marker studies per year for years 1-2 after diagnosis
            ii. No more than 3 bladder tumor marker studies per year for year 3 after diagnosis
            iii. No more than 2 bladder tumor marker studies for year 4 after diagnosis
            iv. No more than 1 bladder tumor marker studies annually for up to 15 years after diagnosis.

III. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for screening of members with hematuria are considered **investigational**.

IV. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for diagnosing, and monitoring bladder cancer are considered **investigational** for all other indications.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis

V. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) FISH panel analysis (88271, 88274, 88275, 88291) in peripheral blood or bone marrow may be considered **medically necessary** when **both** of the following criteria are met:
   A. The panel includes analysis for +12, del(11q), del(13q), and del(17p)
   B. The member is undergoing initial diagnostic workup for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Tumor Specific *ERBB2 (HER2)* Deletion/Duplication (FISH and CISH)

VI. Somatic *ERBB2* (*HER2*) amplification analysis via in situ hybridization (ISH) (i.e., FISH or CISH) (88377) or immunohistochemistry (IHC) (88360) in solid tumors may be considered **medically necessary** when:
   A. The member has **any** of the following:
      1. Recurrent or newly diagnosed stage I-IV invasive breast cancer
      2. Suspected or documented metastatic gastric cancer
      3. Suspected or proven metastatic colorectal cancer or appendiceal adenocarcinoma
      4. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma
      5. Recurrent, unresectable, or metastatic salivary gland tumors
      6. Recurrent, advanced or metastatic cervical carcinoma
      7. Serous endometrial carcinoma
      8. Uterine carcinosarcoma
      9. Resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma
      10. Recurrent ovarian/fallopian tube/primary peritoneal cancer.

Multiple Myeloma FISH Panel Analysis

VII. Multiple myeloma FISH panel analysis (88271, 88273, 88275, 88291) of bone marrow may be considered **medically necessary** when **both** of the following criteria are met:
   A. The panel includes analysis for del(13), del(17p13), t(4;14), t(11;14), t(14;16), t(14;20), 1q21 gain/amplification, del(1p)
   B. The member is undergoing initial diagnostic workup for multiple myeloma.

***NTRK* Fusion Analysis Panel**

VIII. *NTRK 1/2/3* fusion analysis panel (81191, 81192, 81193, 81194) via fluorescent in situ hybridization (FISH) or immunohistochemistry (IHC) in solid tumors may be considered **medically necessary** when:
   A. The member is undergoing initial diagnostic workup for or has a diagnosis of **any** of the following:
      1. Advanced or metastatic lung adenocarcinoma
      2. Advanced or metastatic large cell lung carcinoma
      3. Advanced or metastatic squamous cell lung carcinoma
      4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS)
      5. Unknown primary cancers
      6. Advanced or metastatic colorectal cancer
      7. Cervical sarcoma
      8. Recurrent, progressive, or metastatic vulvar cancer
      9. Recurrent or metastatic endometrial carcinoma
      10. Metastatic uterine sarcoma
      11. Recurrent unresectable or stage IV invasive breast cancer
      12. Unresectable locally advanced, recurrent, or metastatic gastric cancer
      13. Unresectable locally advanced, recurrent, or metastatic esophageal cancer
      14. Anaplastic thyroid carcinoma or locally recurrent, advanced, and/or metastatic papillary, follicular, or oncocytic carcinoma (formerly called Hurthle cell carcinoma)
      15. Acute lymphoblastic leukemia (ALL)
      16. Advanced or metastatic soft tissue sarcoma
      17. Unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm
      18. Metastatic salivary gland tumors

19. Unresectable or metastatic hepatocellular carcinoma
20. Recurrent epithelial ovarian/Fallopian tube/primary peritoneal cancer
21. Metastatic small bowel adenocarcinoma
22. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma
23. Resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma.

Tumor Specific PD-L1 Protein Analysis

IX. PD-L1 protein expression analysis via immunohistochemistry (IHC) (88341, 88342, 88360, 88361) in solid tumors may be considered **medically necessary** when:
   A. The member has a diagnosis of or is in the initial work up stage for **any** of the following:
      1. Stage IB or higher lung adenocarcinoma
      2. Stage IB or higher large cell lung carcinoma
      3. Stage IB or higher squamous cell lung carcinoma
      4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS)
      5. Locally advanced or metastatic bladder cancer
      6. Recurrent, progressive, or metastatic cervical cancer (squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma)
      7. Recurrent or stage IV triple negative breast cancer
      8. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma
      9. Suspected or proven metastatic gastric adenocarcinoma
      10. Recurrent, unresectable, oligometastatic, or metastatic nasopharyngeal cancer
      11. Recurrent, progressive or metastatic vulvar cancer.

Note: PD-L1 protein expression analysis via IHC is often performed as an adjunct component of comprehensive molecular profiling panels for solid tumors

Tumor Specific FOLR1 Protein Analysis

X. Tumor specific FOLR1 protein expression analysis via immunohistochemistry (IHC) analysis (88360) may be considered **medically necessary** when **both** of the following criteria are met:
   A. The member has recurrent, platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer
   B. Elahere (mirvetuximab soravtansine) is being considered for treatment.

Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR)

XI. *PML/RARA* rearrangement analysis via fluorescent in situ hybridization (FISH) (81315, 81316, 88271, 88274, 88275, 88291) in peripheral blood or bone marrow may be considered **medically necessary** when:
   A. The member is undergoing initial diagnostic work up for acute myeloid leukemia (AML).

Tumor Specific *RET* Gene Rearrangement Tests (FISH)

XII. Tumor specific *RET* gene rearrangement testing via fluorescent in situ hybridization (FISH) (88374, 88377, 88271, 88275, 88291) in solid tumors may be considered **medically necessary** when:
   A. The member has a diagnosis of **any** of the following:
      1. Recurrent or persistent locoregional or metastatic medullary thyroid cancer, **AND**
         a. Germline testing for *RET* mutations is negative or has not been done
      2. Anaplastic thyroid carcinoma
      3. Locally recurrent, advanced and/or metastatic papillary thyroid carcinoma
      4. Locally recurrent, advanced and/or metastatic follicular thyroid carcinoma, **OR**
      5. Locally recurrent, advanced and/or metastatic oncocytic carcinoma (formerly called Hurthle cell carcinoma)
      6. Advanced or metastatic adenocarcinoma of the lung

7. Advanced or metastatic large cell cancer of the lung
8. Advanced or metastatic non small-cell cancer of the lung, not otherwise specified
9. Locally advanced or metastatic squamous cell carcinoma of the cervix
10. Locally advanced or metastatic adenocarcinoma of the cervix
11. Locally advanced or metastatic adenosquamous carcinoma of the cervix
12. Recurrent unresectable or stage IV breast cancer
13. Suspected or confirmed metastatic colon cancer
14. Resectable, borderline resectable, locally advanced or metastatic pancreatic adenocarcinoma

Tumor Specific *ROS1* Gene Rearrangement

XIII. Tumor specific *ROS1* gene rearrangement analysis via fluorescent in situ hybridization (FISH) (88271, 88274) in solid tumors may be considered **medically necessary** when:
   A. The member has a diagnosis of **any** of the following:
      1. Advanced or metastatic lung adenocarcinoma
      2. Advanced or metastatic large cell lung carcinoma
      3. Advanced or metastatic squamous cell lung carcinoma
      4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS)
      5. Locally advanced or metastatic ampullary adenocarcinoma
      6. Resectable or borderline resectable, or locally advanced or metastatic pancreatic adenocarcinoma
      7. Pediatric (diagnosed age 18 years or younger) diffuse high-grade glioma.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Definitions

1. **Advanced cancer:** Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.

Coding

See the Codes table for details.

Description

Cytogenetic analysis of solid tumors and hematologic malignancies aims to both classify the type of tumor or cancer present and identify somatic oncogenic mutations in cancer. These mutations, often called "driver" mutations, are becoming increasingly useful for targeted therapy selection, and may give insight into prognosis and treatment response in a subset of cancers. In addition, molecular analysis of solid tumors and hematologic malignancies, in particular, can also aid in making a diagnosis of a specific type of malignancy. For solid tumors, molecular analysis can be performed via direct testing of the tumor (which is addressed in this policy) or via circulating tumor DNA or circulating tumor cells (CTCs) (see Other Related Policies). For hematologic malignancies, molecular analysis can be performed on blood samples or bone marrow biopsy samples (skin or buccal cells/saliva is occasionally used in patients who have received a hematopoietic stem cell transplant).

Related Policies

This policy document provides coverage criteria for oncology-related cytogenetic testing. Please refer to:

- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to DNA testing of a solid tumor or a blood cancer.
- ***Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for coverage criteria related to genetic testing for hereditary cancer predisposition syndromes.
- ***Oncology: Cancer Screening*** for coverage criteria related to the use of non-invasive fecal, urine, or blood tests for screening for cancer.
- ***Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*** for criteria related to circulating tumor DNA (ctDNA) or circulating tumor cell testing performed on peripheral blood for cancer diagnosis, management, and surveillance.
- ***Oncology: Algorithmic (Genetic Expression) Testing*** for coverage criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- ***Genetic Testing: Exome and Genome Sequencing for the Diagnosis of Genetic Disorders*** for coverage criteria related to whole genome and whole exome sequencing in rare genetic syndromes.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to cytogenetic testing in oncology that is not specifically discussed in this or another non-general policy.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

State:
SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

Rationale

Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests
National Comprehensive Cancer Network (NCCN)
The NCCN Thyroid Carcinoma guidelines (4.2023) recommend that individuals with anaplastic thyroid cancer should undergo molecular testing including *BRAF, NTRK, ALK, RET*, MSI, dMMR, and

tumor mutational burden if not previously done (p. ANAP-1). *ALK* testing is also recommended for locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma (p. PAP-10) and locally recurrent, advanced, and/or metastatic follicular thyroid carcinoma (p. FOLL-9).

NCCN Non-Small Cell Lung Cancer guidelines (2.2024) recommend *ALK* rearrangement testing in patients with Stage IB-IIIA, IIIB, disease perioperatively for consideration of systemic therapy (p. NSCL-E, 1 of 3) as well as for patients with advanced or metastatic adenocarcinoma, large cell, squamous cell, or NSCLC not otherwise specified (NOS). (p. NSCL-18)

NCCN guidelines for Ampullary Adenocarcinoma (1.2024) recommend somatic molecular profiling for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*, *FGFR2*, and *RET*), mutations (*BRAF*, *BRCA1/2*, *KRAS*, and *PALB2*), amplifications (HER2), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) via an FDA-approved and/or validated next-generation sequencing (NGS)-based assay. (p. AMP-3)

NCCN guidelines for Histiocytic Neoplasms (1.2023) recommends molecular testing of a tissue biopsy during the diagnostic workup and suggests RNA based molecular panel including fusion testing for *ALK*; however if there is clinical concern for *ALK* rearrangement, or if fusion panel testing is not available, ALK immunohistochemistry and FISH studies may be performed. (p. LCH-2, ECD-2)

NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) recommend somatic molecular profiling for patients with locally advanced/metastatic disease as well as those with resectable or borderline resectable disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*, *FGFR2*, and *RET*), mutations (*BRAF*, *BRCA1/2*, *KRAS*, and *PALB2*), amplifications (HER2), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) via an FDA-approved and/or validated next-generation sequencing (NGS)-based assay. (p. PANC1-A, PANC-F, 1 of 12)

NCCN guidelines for Pediatric Central Nervous System Cancers (2.2023) state that broad molecular testing is required for comprehensive classification of pediatric diffuse high-grade gliomas, including NGS with fusion detection for *ROS1*, *MET*, *NTRK1/2/3*, *ALK*, *FGFR1/2/3*. (p. PEDCNS-B, 2 of 4)

Bladder Cancer Diagnostic and Recurrence FISH Tests

National Comprehensive Cancer Network (NCCN)
NCCN Bladder Cancer guidelines (1.2024) do not currently mention a recommendation for the use of bladder cancer diagnostic and recurrence FISH tests. (e.g., Urovysion)

American Urological Association and Society of Urologic Oncology
The American Urological Association and Society of Urologic Oncology (2016; amended 2020) addressed the diagnosis and treatment of non-muscle-invasive bladder cancer, based on a systematic review and includes the following statements on the use of urine markers after the diagnosis of bladder cancer:

- Urinary biomarker analysis should not replace cystoscopic evaluation in the surveillance of non-muscle invasive bladder cancer (NMIBC). (Strong Recommendation; Evidence Strength: Grade B)
- Urinary biomarker analysis or cytology should not routinely be used during surveillance in a patient with a history of low-risk cancer and a normal cystoscopy. (Expert Opinion)
- Urinary biomarker analysis may be used to assess response to intravesical BCG (UroVysion FISH) and adjudicate equivocal cytology (UroVysion FISH and ImmunoCyt) in a patient with NMIBC. (Expert Opinion) (p. 1024 and 1025)

Note: "Evidence Strength B" describes a recommendation of moderate certainty. "Expert Opinion" is defined in this guideline as "A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence." (p. 1022)

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis
National Comprehensive Cancer Network (NCCN)
NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guidelines (1.2024) recommend FISH testing for the rearrangements specified (at a minimum) during the diagnostic workup for CLL/SLL, including: +12, del(11q), del(13q), and del(17p). (p. CSLL-1)

Tumor Specific *ERBB2* (HER2) Deletion/Duplication (FISH and CISH)
National Comprehensive Cancer Network (NCCN)
NCCN Esophageal and Esophagogastric Junction Cancers guidelines (4.2023) recommend HER2/*ERBB2* testing during the workup of documented or suspected metastatic adenocarcinoma. (p. ESOPH-1)

NCCN Head and Neck Cancers guidelines (2.2024) recommend HER2/*ERBB2* testing for therapeutic options for individuals diagnosed with recurrent, unresectable, or metastatic salivary gland tumors. (p. SALI-B 1 of 2)

NCCN Colon Cancer guidelines (1.2024) recommend HER2/*ERBB2* testing during the workup for suspected or proven metastatic colorectal cancer. (p. COL-2) These guidelines also recommend HER2 analysis for metastatic appendiceal adenocarcinoma. (p. COL-I 2 of 3)

NCCN Gastric Cancer guidelines (3.2023) recommend HER2/*ERBB2* testing for patients with suspected or documented metastatic disease. (p. GAST-1)

NCCN Breast Cancer guidelines (1.2024) recommend HER2/*ERBB2* testing be performed on all patients with newly diagnosed primary or metastatic breast cancer. (p. BINV-A 1 of 2)
NCCN Cervical Cancer guidelines (1.2024) recommend HER2 testing for recurrent, advanced or metastatic cervical carcinoma. (p. CERV-A 1 of 7)

NCCN Uterine Neoplasms guidelines (1.2024) recommend HER2 IHC with reflex to FISH for all serous and carcinosarcoma uterine tumors. (p. ENDO-A, 1 of 4)

NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) indicate that testing for potentially actionable somatic findings including HER2 amplifications should be considered for resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-C, 1 of 12) as well as in locally advanced/metastatic disease (p. PANC-1A).

NCCN guidelines for Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (1.2024) recommend HER2 testing by IHC for recurrent disease after primary treatment (p. OV-6)

Multiple Myeloma FISH Panel Analysis
National Comprehensive Cancer Network (NCCN)
NCCN Multiple Myeloma guidelines (2.2024) recommend FISH testing during the initial workup of multiple myeloma for prognostic purposes. The recommended FISH testing includes: del(13), del (17p13), t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/1q21 amplification, 1p deletion. (p. MYEL-1)

***NTRK* Fusion Analysis Panel**
National Comprehensive Cancer Network (NCCN)
The NCCN Thyroid Carcinoma guidelines (4.2023) recommend that individuals with anaplastic thyroid cancer or locally recurrent, advanced, and/or metastatic papillary, follicular, and oncocytic

carcinoma (formerly called Hurthle cell carcinoma) undergo molecular testing as part of disease workup. Oncocytic carcinoma should undergo molecular testing including *BRAF, NTRK, ALK, RET*, MSI, dMMR, and tumor mutational burden if not previously done. (p. ANAP-1, p. PAP-9, p. FOLL-8, p. ONC-9)

The NCCN Colon Cancer Guidelines (1.2024) state that studies have estimated that about 0.2% to 1% of CRCs carry *NTRK* gene fusions. Two targeted therapies, larotrectinib and entrectinib, have been FDA-approved for the treatment of patients with metastatic, unresectable solid tumors that have an *NTRK* gene fusion and no satisfactory alternative treatment options, regardless of the location of the primary tumor. (p. MS-70)

The NCCN Non-Small Cell Lung Cancer guidelines (2.2024) recommends *NTRK* fusion analysis for patients with advanced or metastatic adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and NSCLC not otherwise specified (NOS). (p. NSCL-18)

The NCCN Occult Primary guidelines (1.2024) states that patients with metastatic or unresectable *NTRK* gene fusion positive adenocarcinomas without a known acquired resistance mutation, who have no satisfactory treatment options or who have progressed on treatment can be treated with larotrectinib (p. OCC-B, 2 of 11).

The NCCN Cervical Cancer guidelines (1.2024) recommends *NTRK* fusion analysis for patients with cervical sarcoma. (p. CERV-A 1 of 7).

The NCCN Vulvar Cancer guidelines (3.2024) recommends *NTRK* fusion analysis for recurrent, progressive, or metastatic vulvar cancer. (p. VULVA-A 1 of 3)

The NCCN Uterine Neoplasms guidelines (1.2024) advises to consider *NTRK* fusion analysis for recurrent or metastatic endometrial carcinoma (p. ENDO-A 2 of 4) or metastatic uterine sarcoma. (p. UTSARC-A 1 of 8)

The NCCN Breast Cancer guidelines (1.2024) indicate that patients whose tumors have an *NTRK* gene fusion without a known acquired resistance mutation and have no other satisfactory treatment options or have progressed following treatment can receive larotrectinib or entrectinib (p. BINV-Q, 6 of 14).

The NCCN Gastric Cancer guidelines (3.2023) recommends *NTRK* fusion analysis for unresectable locally advanced, recurrent, or metastatic gastric cancer. (p. GAST-B 5 of 6, p. GAST-F 4 of 16)
The NCCN Esophageal and Esophagogastric Junction Cancer guidelines (4.2023) recommends *NTRK* fusion analysis for unresectable, locally advanced, recurrent, or metastatic esophageal cancer. (p. ESOPH-B 5 of 6, p. ESOPH-F 4 of 17)

The NCCN Acute Lymphoblastic Leukemia guidelines (3.2023) and Pediatric Acute Lymphoblastic Leukemia guidelines (3.2024) recommend *NTRK* fusion analysis for acute lymphoblastic leukemia (ALL). (p. ALL-A 1 of 2; p. PEDALL-A)
The NCCN Soft Tissue Sarcoma guidelines (3.2023) state that larotrectinib and entrectinib have demonstrated efficacy in patients with *NTRK* positive tumors and are recommended as first line treatment options for patients with advanced or metastatic *NTRK* positive sarcomas. (p. MS-29)
The NCCN Neuroendocrine and Adrenal Tumors guidelines (1.2023) recommends *NTRK* fusion testing for patients with unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm. (p. PDNEC-1)

The NCCN Head and Neck Cancers guidelines (2.2024) mention use of NGS profiling and other appropriate biomarker testing to evaluate *NTRK* prior to treatment for metastatic salivary gland tumors (p. SALI-4).

The NCCN Hepatocellular Carcinoma guidelines (2.2023) indicate that *NTRK1/NTRK2/NTRK3* fusions have not been reported in HCC. However, as studies have demonstrated response rates in the 57% to 75% range in pre-treated *NTRK* fusion-positive tumors, larotrectinib and entrectinib are subsequent-line systemic therapy options for patients with HCC that is *NTRK* gene fusion positive. (p. MS-37).
The NCCN Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer guidelines (1.2024) recommend tumor molecular testing including *NTRK* testing for recurrent disease if prior testing did not include these markers (p. OV-6)

The NCCN Small Bowel Adenocarcinoma guidelines (1.2024) recommends larotrectinib and entrectinib as options for subsequent-line treatment of metastatic small bowel adenocarcinoma that is *NTRK* gene fusion positive (p. MS-15).

The NCCN Pediatric Central Nervous System Cancers guidelines (2.2023) state that broad molecular testing is required for comprehensive classification of pediatric diffuse high-grade gliomas, including NGS with fusion detection for *ROS1*, *MET*, *NTRK1/2/3*, *ALK*, *FGFR1/2/3*. (p. PEDCNS-B, 2 of 4)
NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) indicate that testing for potentially actionable somatic findings including *NTRK* fusions should be considered for resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-C, 1 of 12) as well as in locally advanced/metastatic disease (p. PANC-1A).

Tumor Specific PD-L1 Protein Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN Gastric Cancer guidelines (3.2023) recommends PD-L1 testing during the workup for documented or suspected metastatic adenocarcinoma. (p. GAST-1)

The NCCN Head and Neck Cancers guidelines (2.2024) recommends PD-L1 testing during the workup phase for recurrent, unresectable, oligometastatic, or metastatic cancer of the nasopharynx. (p. NASO-B 1 of 3)

The NCCN Bladder Cancer guidelines (1.2024) recommend PD-L1 testing in individuals with locally advanced or metastatic (stage IV) bladder cancer to guide medical management. (p. BL-G 2 of 7)
The NCCN Vulvar Cancer guidelines (3.2024) recommends PD-L1 testing for individuals with recurrent, progressive, or metastatic vulvar cancer. (p. VULVA-A 1 of 3)

The NCCN Esophageal and Esophagogastric Junction Cancers guidelines (4.2023) recommends PD-L1 testing for individuals during the workup phase for documented or suspected metastatic esophageal and esophagogastric junction cancers. (p. ESOPH-1)

The NCCN Cervical Cancer guidelines (1.2024) recommends PD-L1 testing for individuals with recurrent, progressive, or metastatic cervical cancer of the following pathologies: squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. (p. CERV-A 1 of 3)

NCCN Non-Small Cell Lung Cancer guidelines (2.2024) recommend PD-L1 testing in patients with stage IB-IIIA, IIIB non-small cell lung cancer perioperatively (p. NSCL-E, 1 of 3) or for advanced or metastatic adenocarcinoma, large cell, squamous cell, and NSCLC not otherwise specified (NOS). (p. NSCL-18)

The NCCN Breast Cancer guidelines (1.2024) recommends PD-L1 testing for individuals with recurrent or stage IV triple negative breast cancer. (p. BINV-R 1 of 3)

Tumor Specific FOLR1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (1.2024) indicate that the preferred treatment regimen for platinum resistant recurrent disease includes mirvetuximab soravtansine if the tumor expresses folate receptor alpha (i.e., FOLR1). Therefore, tumor molecular analysis for this cancer type is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit, including folate receptor alpha (FOLR1) (p. OV-C, 9 and 10 of 11).

In the setting of recurrent disease, tumor molecular analysis is also recommended to include folate receptor alpha (FOLR1) if prior testing did not include this marker (p. OV-6).

Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR)

National Comprehensive Cancer Network (NCCN)

NCCN Acute Myeloid Leukemia guidelines (6.2023) state that many different types of gene mutations are associated with specific prognoses, helping to guide medical management decisions, and/or may indicate that specific therapeutic agents are useful. Therefore, all patients with AML should be tested for these mutations. (p. EVAL-1A). The discussion section of this guideline states that *PML-RAR* alpha is included in this group of genetic markers that should be tested in all patients. (p. MS-3)

Tumor Specific *RET* Gene Rearrangement (FISH)

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Thyroid Carcinoma (4.2023) recommend molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS. Germline and somatic *RET* testing is recommended in all individuals with newly diagnosed medullary thyroid carcinoma. For patients with recurrent or persistent MTC, somatic *RET* testing is recommended if germline wild type or germline unknown (p. MEDU-6). Additionally they comment that molecular testing has shown to be beneficial when making targeted therapy decisions. (p. THYR-B) The guideline also comments that individuals with anaplastic thyroid cancer and/or metastatic disease should undergo molecular testing including *BRAF*, *NTRK*, *ALK*, *RET* and tumor mutational burden if not previously done. (p. ANAP-3)

The NCCN guideline on Non-Small Cell Lung Cancer (2.2024) recommends analysis for *RET* gene rearrangements, noting that NGS-based methodology has a high specificity and that RNA-based NGS is preferable to DNA-based NGS for fusion detection. (p. NSCL-H, 5 of 7)

The NCCN guideline for Cervical Cancer (1.2024) suggests performing *RET* gene fusion testing for patients with locally advanced or metastatic cervical cancer of the following pathologies: squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. (p. CERV-A, 1 of 3)

NCCN guidelines for Breast Cancer (1.2024) list *RET* fusion as a biomarker with an FDA approved therapy for any subtype of recurrent unresectable or stage IV disease. Either tumor tissue or blood can be used for detection. (p. BINV-Q, 6 of 14).

NCCN guidelines for Colon Cancer (1.2024) discuss *RET* fusion detection as part of the workup for suspected or proven metastatic adenocarcinoma (p. COL-2). Testing should be done via broad molecular profiling to identify rare and actionable mutations and fusions.

NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) indicate that testing for potentially actionable somatic findings including *RET* fusions should be considered for resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-C, 1 of 12) as well as in locally advanced/metastatic disease (p. PANC-1A).

Tumor Specific *ROS1* Gene Rearrangement

National Comprehensive Cancer Network (NCCN)
NCCN Non-Small Cell Lung Cancer guidelines (5.2023) recommend *ROS1* rearrangement testing in patients with advanced or metastatic disease of the following lung cancer pathologies: Adenocarcinoma, Large Cell, Squamous Cell, and NSCLC not otherwise specified (NOS). (p. NSCL-18)
NCCN guidelines for Ampullary Adenocarcinoma (1.2024) recommend tumor molecular profiling for patients with locally advanced or metastatic disease. Potentially actionable somatic findings include fusions involving the *ROS1* gene. (p. AMP-3)

NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) recommend tumor molecular profiling for patients with resectable, borderline resectable, or locally advanced or metastatic disease. Potentially actionable somatic findings include fusions involving the *ROS1* gene. (p. PANC-1A, PANC-F, 1 of 12).
NCCN guidelines for Pediatric Central Nervous System Cancers (2.2023) state that broad molecular testing is required for comprehensive classification of pediatric diffuse high-grade gliomas and should include detection of fusions involving *ROS1*. (p. PEDCNS-B, 2 of 4).

Centers for Medicare and Medicaid Services
The CMS local coverage determination (LCD) entitled "Lab: Bladder/Urothelial Tumor Markers" includes the following utilization guidelines for bladder marker testing.
Regarding the UroVysion Bladder Cancer Kit: "It is used to detect chromosomal abnormalities in voided urine to assist not only in bladder cancer surveillance but also in the initial identification of bladder cancer."

"*Follow-up after initial diagnosis/most recent occurrence and treatment*

- Maximum of 4 bladder tumor marker studies per year for years 1-2
- Maximum of 3 bladder tumor marker studies per year for year 3
- Maximum of 2 bladder tumor marker studies for year 4 and
- Maximum of 1 bladder tumor marker studies follow-up annually for up to 15 years."

"For high risk patients with persistent hematuria and a negative FISH assay following a comprehensive diagnostic (no tumor identified) workup, ONE repeat FISH testing in conjunction with cystoscopy is considered reasonable and necessary within 1 year of the original attempted diagnosis."

The CMS LCD Reference Article "Billing and Coding: Lab: Bladder/Urothelial Tumor Markers" states the following: "This A/B MAC will only cover bladder tumor marker fluorescence in situ hybridization (FISH) testing services when performed using validated assays. To date, UroVysion Bladder Cancer Kit is the only Federal Drug Administration (FDA) approved assay that is designed to detect aneuploidy for chromosomes 3, 7, 17 and loss of the 9p21 locus via FISH.

Bladder cancer tumor markers performed by any technology, immunoassay, molecular or FISH testing, are not covered for screening of all patients with hematuria."

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Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier. The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis
	81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis
	81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis
	81194	NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis
	81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis; common breakpoints (e.g., intron 3 and intron 6), qualitative or quantitative
	81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis; single breakpoint (e.g., intron 3, intron 6 or exon 6), qualitative or quantitative
	88120	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
	88121	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology
	88237	Tissue culture for neoplastic disorders; bone marrow, blood cells
	88271	Molecular cytogenetics; DNA probe, each (e.g., FISH)
	88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
	88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
	88291	Cytogenetics and molecular cytogenetics, interpretation and report
	88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
	88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
	88360	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
	88361	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology
	88374	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each multiplex probe stain procedure
	88377	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; each multiplex probe stain procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/01/2023	New policy.
07/01/2024	Annual review. Policy statement, guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local

standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
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Oncology: Cytogenetic Testing BSC_CON_2.11 **Policy Statement:** **Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests** I. Somatic *ALK* rearrangement analysis (88271, 88274) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of or is in the initial work up stage for **any** of the following: 1. Stage IB or higher lung adenocarcinoma 2. Stage IB or higher large cell lung carcinoma 3. Stage IB or higher squamous cell lung carcinoma 4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS) 5. Anaplastic thyroid carcinoma 6. Locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma 7. Locally recurrent, advanced, and/or metastatic follicular thyroid cancer **Tumor Specific *BCR/ABL1* Gene Rearrangement (Qualitative FISH and PCR) Tests** II. Tumor specific *BCR/ABL1* rearrangement analysis via fluorescent in situ hybridization (FISH) (88271, 88274, 88275, 88291) or PCR (81206,	**Oncology: Cytogenetic Testing BSC_CON_2.11** **Policy Statement:** **Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests** I. Somatic *ALK* rearrangement analysis (88271, 88274) in solid tumors is considered **medically necessary** when: A. The member has a diagnosis of or is in the initial work up stage for **any** of the following: 1. Stage IB or higher lung adenocarcinoma 2. Stage IB or higher large cell lung carcinoma 3. Stage IB or higher squamous cell lung carcinoma 4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS) 5. Anaplastic thyroid carcinoma 6. Locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma 7. Locally recurrent, advanced, and/or metastatic follicular thyroid cancer 8. Locally advanced/metastatic ampullary adenocarcinoma 9. Langerhans cell histiocytosis 10. Erdheim-Chester disease 11. Resectable, borderline resectable or locally advanced or metastatic pancreatic adenocarcinoma 12. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma.

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81207, 81208, 81479) in peripheral blood or bone marrow may be considered **medically necessary** when the member meets **either** of the following: A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, or chronic myeloid leukemia) B. The member is undergoing diagnostic workup for **any** of the following: 1. Acute lymphoblastic leukemia (ALL) 2. Acute myeloid leukemia (AML) 3. Chronic myeloid leukemia (CML) 4. B-cell lymphoma **Note**: Refer to Blue Shield of California Medical Policy: *Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies* for coverage criteria regarding minimal residual disease (MRD) indications for *BCR/ABL1* to monitor disease progression. **Bladder Cancer Diagnostic and Recurrence FISH Tests** III. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for screening, diagnosing, and monitoring bladder cancer are considered **investigational**.	**Bladder Cancer Diagnostic and Recurrence FISH Tests** II. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for diagnosing, and monitoring bladder cancer may be considered **medically necessary** when: A. The member meets **one** of the following: 1. The member has hematuria, **AND both** of the following: a. Diagnostic studies have failed to identify the etiology of the hematuria b. A bladder cancer diagnostic and recurrence FISH test has not been ordered more than 1 time in the past 12 months, **OR** 2. The member has been treated for bladder cancer, **AND** a. The bladder cancer diagnostic and recurrence FISH tests are ordered with **any** of the following frequency: i. No more than 4 bladder tumor marker studies per year for years 1-2 after diagnosis

POLICY STATEMENT	
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	ii. No more than 3 bladder tumor marker studies per year for year 3 after diagnosis iii. No more than 2 bladder tumor marker studies for year 4 after diagnosis iv. No more than 1 bladder tumor marker studies annually for up to 15 years after diagnosis. III. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for screening of members with hematuria are considered **investigational**. IV. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for diagnosing, and monitoring bladder cancer are considered **investigational** for all other indications.
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis IV. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) FISH panel analysis (88271, 88274, 88275, 88291) in peripheral blood or bone marrow may be considered **medically necessary** when **both** of the following criteria are met: A. The panel includes analysis for +12, del(11q), del(13q), and del(17p) B. The member is undergoing initial diagnostic workup for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	**Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis** V. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) FISH panel analysis (88271, 88274, 88275, 88291) in peripheral blood or bone marrow may be considered **medically necessary** when **both** of the following criteria are met: A. The panel includes analysis for +12, del(11q), del(13q), and del(17p) B. The member is undergoing initial diagnostic workup for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).
Tumor Specific *ERBB2 (HER2)* Deletion/Duplication (FISH and CISH) V. Somatic *ERBB2 (HER2)* amplification analysis via in situ hybridization (ISH) (i.e., FISH or CISH) or immunohistochemistry (IHC) (88360, 88377) in solid tumors may be considered **medically necessary** when: A. The member has **any** of the following: 1. Recurrent or newly diagnosed stage I-IV invasive breast cancer 2. Inoperable locally advanced, recurrent, or metastatic gastric cancer and trastuzumab (or FDA-approved equivalent medication) is being considered for treatment	**Tumor Specific *ERBB2 (HER2)* Deletion/Duplication (FISH and CISH)** VI. Somatic *ERBB2* (*HER2*) amplification analysis via in situ hybridization (ISH) (i.e., FISH or CISH) (88377) or immunohistochemistry (IHC) (88360) in solid tumors may be considered **medically necessary** when: A. The member has **any** of the following: 1. Recurrent or newly diagnosed stage I-IV invasive breast cancer 2. Suspected or documented metastatic gastric cancer

POLICY STATEMENT	
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3. Suspected or proven metastatic colorectal cancer or documented metachronous metastases by CT, MRI, and/or biopsy 4. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma 5. Recurrent, unresectable, or metastatic salivary gland tumors.	3. Suspected or proven metastatic colorectal cancer or appendiceal adenocarcinoma 4. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma 5. Recurrent, unresectable, or metastatic salivary gland tumors 6. Recurrent, advanced or metastatic cervical carcinoma 7. Serous endometrial carcinoma 8. Uterine carcinosarcoma 9. Resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma 10. Recurrent ovarian/fallopian tube/primary peritoneal cancer.
Multiple Myeloma FISH Panel Analysis VI. Multiple myeloma FISH panel analysis (88271, 88273, 88275, 88291) of bone marrow may be considered **medically necessary** when **both** of the following criteria are met: A. The panel includes analysis for del(13), del(17p13), t(4;14), t(11;14), t(14;16), t(14;20), 1q21 gain/amplification, del(1p) B. The member is undergoing initial diagnostic workup for multiple myeloma.	**Multiple Myeloma FISH Panel Analysis** VII. Multiple myeloma FISH panel analysis (88271, 88273, 88275, 88291) of bone marrow may be considered **medically necessary** when **both** of the following criteria are met: A. The panel includes analysis for del(13), del(17p13), t(4;14), t(11;14), t(14;16), t(14;20), 1q21 gain/amplification, del(1p) B. The member is undergoing initial diagnostic workup for multiple myeloma.
***NTRK* Fusion Analysis Panel** VII. *NTRK 1/2/3* fusion analysis panel (81191, 81192, 81193, 81194) via fluorescent in situ hybridization (FISH) or immunohistochemistry (IHC) in solid tumors may be considered **medically necessary** when: A. The member is undergoing initial diagnostic workup for or has a diagnosis of **any** of the following: 1. Advanced or metastatic lung adenocarcinoma 2. Advanced or metastatic large cell lung carcinoma 3. Advanced or metastatic squamous cell lung carcinoma	***NTRK* Fusion Analysis Panel** VIII. *NTRK 1/2/3* fusion analysis panel (81191, 81192, 81193, 81194) via fluorescent in situ hybridization (FISH) or immunohistochemistry (IHC) in solid tumors may be considered **medically necessary** when: A. The member is undergoing initial diagnostic workup for or has a diagnosis of **any** of the following: 1. Advanced or metastatic lung adenocarcinoma 2. Advanced or metastatic large cell lung carcinoma 3. Advanced or metastatic squamous cell lung carcinoma 4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS)

POLICY STATEMENT	
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4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS) 5. Unknown primary cancers 6. Advanced or metastatic colorectal cancer 7. Cervical sarcoma 8. Recurrent, progressive, or metastatic vulvar cancer 9. Recurrent or metastatic endometrial carcinoma or a diagnosis of uterine sarcoma 10. Recurrent unresectable or stage IV invasive breast cancer 11. Unresectable locally advanced, recurrent, or metastatic gastric cancer 12. Unresectable locally advanced, recurrent, or metastatic esophageal cancer 13. Anaplastic thyroid carcinoma or locally recurrent, advanced, and/or metastatic papillary, follicular, or Hurthle cell thyroid carcinoma 14. Acute lymphoblastic leukemia (ALL) 15. Soft tissue sarcoma 16. Unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm	5. Unknown primary cancers 6. Advanced or metastatic colorectal cancer 7. Cervical sarcoma 8. Recurrent, progressive, or metastatic vulvar cancer 9. Recurrent or metastatic endometrial carcinoma 10. Metastatic uterine sarcoma 11. Recurrent unresectable or stage IV invasive breast cancer 12. Unresectable locally advanced, recurrent, or metastatic gastric cancer 13. Unresectable locally advanced, recurrent, or metastatic esophageal cancer 14. Anaplastic thyroid carcinoma or locally recurrent, advanced, and/or metastatic papillary, follicular, or oncocytic carcinoma (formerly called Hurthle cell carcinoma) 15. Acute lymphoblastic leukemia (ALL) 16. Advanced or metastatic soft tissue sarcoma 17. Unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm 18. Metastatic salivary gland tumors 19. Unresectable or metastatic hepatocellular carcinoma 20. Recurrent epithelial ovarian/Fallopian tube/primary peritoneal cancer 21. Metastatic small bowel adenocarcinoma 22. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma 23. Resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma.
Tumor Specific *PD-L1* Protein Analysis	**Tumor Specific PD-L1 Protein Analysis**

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VIII. *PD-L1* protein expression analysis via immunohistochemistry (IHC) (88341, 88342, 88360, 88361) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of or is in the initial work up stage for **any** of the following: 1. Stage IB or higher lung adenocarcinoma 2. Stage IB or higher large cell lung carcinoma 3. Stage IB or higher squamous cell lung carcinoma 4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS) 5. Locally advanced or metastatic bladder cancer 6. Recurrent, progressive, or metastatic cervical cancer (squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma) 7. Recurrent or stage IV triple negative breast cancer 8. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma 9. Suspected or proven metastatic gastric adenocarcinoma 10. Recurrent, unresectable, oligometastatic, or metastatic nasopharyngeal cancer 11. Recurrent, progressive or metastatic vulvar cancer **Note**: PD-L1 protein expression analysis via IHC is often performed as an adjunct component of comprehensive molecular profiling panels for solid tumors	IX. PD-L1 protein expression analysis via immunohistochemistry (IHC) (88341, 88342, 88360, 88361) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of or is in the initial work up stage for **any** of the following: 1. Stage IB or higher lung adenocarcinoma 2. Stage IB or higher large cell lung carcinoma 3. Stage IB or higher squamous cell lung carcinoma 4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS) 5. Locally advancedor metastatic bladder cancer 6. Recurrent, progressive, or metastatic cervical cancer (squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma) 7. Recurrent or stage IV triple negative breast cancer 8. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma 9. Suspected or proven metastatic gastric adenocarcinoma 10. Recurrent, unresectable, oligometastatic, or metastatic nasopharyngeal cancer 11. Recurrent, progressive or metastatic vulvar cancer. **Note**: PD-L1 protein expression analysis via IHC is often performed as an adjunct component of comprehensive molecular profiling panels for solid tumors
Tumor Specific FOLR1 Protein Analysis IX. Tumor specific FOLR1 protein expression analysis via immunohistochemistry (IHC) analysis (88360) may be considered **medically necessary** when **both** of the following criteria are met: A. The member has a diagnosis of epithelial ovarian, fallopian tube or primary peritoneal cancer B. Elahere (mirvetuximab soravtansine) is being considered for treatment	**Tumor Specific FOLR1 Protein Analysis** X. Tumor specific FOLR1 protein expression analysis via immunohistochemistry (IHC) analysis (88360) may be considered **medically necessary** when **both** of the following criteria are met: A. The member has recurrent, platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer B. Elahere (mirvetuximab soravtansine) is being considered for treatment.

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Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR) X. *PML/RARA* rearrangement analysis via fluorescent in situ hybridization (FISH) (81315, 81316, 88271, 88274, 88275, 88291) in peripheral blood or bone marrow may be considered **medically necessary** when: A. The member is undergoing initial diagnostic work up for acute myeloid leukemia (AML). **Tumor Specific RET Gene Rearrangement Tests (FISH)** XI. Tumor specific *RET* gene rearrangement testing (88374, 88377, 88271, 88275, 88291) in solid tumors may be considered **medically necessary** when the member has **any** of the following: A. The member has a diagnosis of recurrent or persistent locoregional or metastatic medullary thyroid cancer and germline testing for RET mutations is negative or has not been done B. The member has a diagnosis of anaplastic thyroid carcinoma C. The member has or locally recurrent, advanced and/or metastatic papillary thyroid carcinoma D. The member has locally recurrent, advanced and/or metastatic follicular thyroid carcinoma E. The member has locally recurrent, advanced and/or metastatic Hurthle cell thyroid carcinoma F. The member has a diagnosis of advanced or metastatic adenocarcinoma of the lung G. The member has a diagnosis of advanced or metastatic large cell cancer of the lung H. The member has a diagnosis of advanced or metastatic non small-cell cancer of the lung, not otherwise specified I. The member has locally advanced or metastatic squamous cell carcinoma of the cervix J. The member has locally advanced or metastatic adenocarcinoma of the cervix	**Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR)** XI. *PML/RARA* rearrangement analysis via fluorescent in situ hybridization (FISH) (81315, 81316, 88271, 88274, 88275, 88291) in peripheral blood or bone marrow may be considered **medically necessary** when: A. The member is undergoing initial diagnostic work up for acute myeloid leukemia (AML). **Tumor Specific *RET* Gene Rearrangement Tests (FISH)** XII. Tumor specific *RET* gene rearrangement testing via fluorescent in situ hybridization (FISH) (88374, 88377, 88271, 88275, 88291) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Recurrent or persistent locoregional or metastatic medullary thyroid cancer, **AND** a. Germline testing for *RET* mutations is negative or has not been done 2. Anaplastic thyroid carcinoma 3. Locally recurrent, advanced and/or metastatic papillary thyroid carcinoma 4. Locally recurrent, advanced and/or metastatic follicular thyroid carcinoma, **OR** 5. Locally recurrent, advanced and/or metastatic oncocytic carcinoma (formerly called Hurthle cell carcinoma) 6. Advanced or metastatic adenocarcinoma of the lung 7. Advanced or metastatic large cell cancer of the lung 8. Advanced or metastatic non small-cell cancer of the lung, not otherwise specified 9. Locally advanced or metastatic squamous cell carcinoma of the cervix 10. Locally advanced or metastatic adenocarcinoma of the cervix 11. Locally advanced or metastatic adenosquamous carcinoma of the cervix 12. Recurrent unresectable or stage IV breast cancer

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K. The member has locally advanced or metastatic adenosquamous carcinoma of the cervix. **Tumor Specific *ROS1* Gene Rearrangement** XII. Somatic *ROS1* rearrangement analysis via fluorescent in situ hybridization (FISH) (88271, 88274) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Advanced or metastatic lung adenocarcinoma 2. Advanced or metastatic large cell lung carcinoma 3. Advanced or metastatic squamous cell lung carcinoma 4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS)	13. Suspected or confirmed metastatic colon cancer 14. Resectable, borderline resectable, locally advanced or metastatic pancreatic adenocarcinoma **Tumor Specific *ROS1* Gene Rearrangement** XIII. Tumor specific *ROS1* gene rearrangement analysis via fluorescent in situ hybridization (FISH) (88271, 88274) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Advanced or metastatic lung adenocarcinoma 2. Advanced or metastatic large cell lung carcinoma 3. Advanced or metastatic squamous cell lung carcinoma 4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS) 5. Locally advanced or metastatic ampullary adenocarcinoma 6. Resectable or borderline resectable, or locally advanced or metastatic pancreatic adenocarcinoma 7. Pediatric (diagnosed age 18 years or younger) diffuse high-grade glioma.