BSC_CON_2.11	Oncology: Cytogenetic Testing		
Original Policy Date:	December 1, 2023	**Effective Date:**	January 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 26

Example Test Table

The tests, associated laboratories, CPT codes, and ICD 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 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* FISH, Non-Small cell Lung Cancer (Labcorp)	88271, 88274
Bladder Cancer Diagnostic and Recurrence FISH Tests	UroVysion Bladder Kit (Quest Diagnostics)	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)	88237, 88271, 88275, 88291
	Multiple Myeloma (MM) Profile, FISH (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, APL, *PML/RARA*, Translocation 15, 17 (Quest Diagnostics)	81315, 81316, 88271, 88274, 88275, 88291
	PML/RARA t(15;17) (NeoGenomics Laboratories)	
Tumor Specific *RET* Gene Rearrangement (FISH)	RET FISH (NeoGenomics Laboratories)	88271, 88275, 88291, 88374, 88377
	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 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
      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 has hematuria, **AND**
      1. Diagnostic studies have failed to identify the etiology of the hematuria, **AND**
      2. A bladder cancer diagnostic and recurrence FISH test has not been ordered more than 1 time in the past 12 months, **OR**
   B. The member has been treated for bladder cancer, **AND**
      1. The bladder cancer diagnostic and recurrence FISH tests are ordered with the following frequency:
         a. No more than 4 bladder tumor marker studies per year for years 1 to 2 after diagnosis
         b. No more than 3 bladder tumor marker studies per year during year 3 after diagnosis
         c. No more than 2 bladder tumor marker studies during year 4 after diagnosis
         d. 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 to IV invasive breast cancer
      2. Inoperable locally advanced, recurrent or metastatic gastric cancer
      3. Suspected or proven metastatic colorectal cancer or appendiceal adenocarcinoma
      4. Inoperable locally advanced, recurrent or metastatic esophageal and/or esophagogastric junction adenocarcinoma
      5. Recurrent, unresectable, or metastatic salivary gland tumors, **OR**
      6. Recurrent, advanced or metastatic cervical carcinoma
      7. Serous endometrial carcinoma
      8. Endometrial carcinosarcoma
      9. p53 abnormal endometrial carcinoma
      10. Resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma
      11. Recurrent ovarian/fallopian tube/primary peritoneal cancer
      12. Recurrent or metastatic vaginal cancer
      13. Stage IIIB or higher muscle invasive bladder cancer
      14. Metastatic small bowel adenocarcinoma.

Multiple Myeloma FISH Panel Analysis

VII. Multiple myeloma FISH panel analysis (88237, 88271, 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:
      1. Advanced, progressive, or metastatic solid tumor, **OR**
      2. Cancer for which surgical resection is not possible, **OR**
      3. Unknown primary cancers, **OR**
   B. The member has a diagnosis of any of the following cancers at any stage:
      1. Cervical sarcoma, **OR**
      2. Anaplastic thyroid carcinoma, **OR**
      3. Acute lymphoblastic leukemia (ALL), **OR**
      4. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma.

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 unresectable or stage IV triple negative breast cancer
8. Locally advanced, recurrent or metastatic esophageal and/or esophagogastric junction adenocarcinoma
9. Locally advanced, recurrent or metastatic gastric adenocarcinoma, **OR**
10. Recurrent, unresectable, oligometastatic, or metastatic nasopharyngeal cancer
11. Recurrent, progressive or metastatic squamous cell vulvar cancer
12. Recurrent or metastatic vaginal 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:
      1. Recurrent or persistent locoregional or metastatic medullary thyroid cancer, **AND**
         a. Germline testing for *RET* mutations is negative or has not been done, **OR**
      2. Anaplastic thyroid carcinoma, **OR**
      3. Locally recurrent, advanced and/or metastatic papillary thyroid carcinoma, **OR**
      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), **OR**
      6. Advanced or metastatic adenocarcinoma of the lung, **OR**
      7. Advanced or metastatic large cell cancer of the lung, **OR**
      8. Advanced or metastatic non-small cell cancer of the lung, not otherwise specified, **OR**
      9. Locally advanced or metastatic squamous cell carcinoma of the cervix, **OR**
      10. Locally advanced or metastatic adenocarcinoma of the cervix, **OR**
      11. Locally advanced or metastatic adenosquamous carcinoma of the cervix, **OR**
      12. Recurrent unresectable or stage IV breast cancer, **OR**
      13. Suspected or confirmed metastatic colon cancer, **OR**
      14. Resectable, borderline resectable, locally advanced or metastatic pancreatic adenocarcinoma, **OR**
      15. Locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer, **OR**
      16. Locally advanced, recurrent or metastatic gastric cancer, **OR**
      17. Recurrent or metastatic vaginal cancer.

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 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 (3.2024) 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 (7.2024) recommend *ALK* rearrangement testing in patients with Stage IB-IIIA, IIIB [T3,N2] disease perioperatively for consideration of systemic therapy (p. NSCL-E, 1 of 5) as well as for patients with advanced or metastatic adenocarcinoma, large cell, squamous cell, or NSCLC not otherwise specified (NOS). (p. NSCL-19)

NCCN guidelines for Ampullary Adenocarcinoma (2.2024) recommend somatic molecular profiling for patients with locally advanced/metastatic disease if systemic therapy is being considered. Potentially actionable somatic findings include fusions involving the ALK gene. (p. AMP-3)

NCCN guidelines for Histiocytic Neoplasms (2.2024) recommends molecular testing of a tissue biopsy during the diagnostic workup for Langerhans cell histiocytosis and Erdheim-Chester disease, and

suggests RNA based molecular panel including fusion testing for *ALK*; however if *ALK* rearrangement is suspected clinically, 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 (3.2024) recommend somatic molecular profiling for patients with locally advanced/metastatic disease as well as those with resectable or borderline resectable disease if systemic therapy is being considered. Potentially actionable somatic findings include fusions involving the ALK gene. (p. PANC-1A)

NCCN guidelines for Pediatric Central Nervous System Cancers (1.2024) recommend broad molecular testing to classify pediatric diffuse high-grade gliomas. This includes detection of fusions involving the ALK gene. (p. PGLIO-B, 2 of 4)

Bladder Cancer Diagnostic and Recurrence FISH Tests
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."

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis
National Comprehensive Cancer Network (NCCN)
NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guidelines (3.2024) recommend FISH testing for +12; del(11q); del(13q); del(17p) during the diagnostic workup for CLL/SLL as this information is useful for prognosis and treatment planning. (p. CSLL-1)

Tumor Specific *ERBB2* (HER2) Deletion/Duplication (FISH and CISH)
National Comprehensive Cancer Network (NCCN)
NCCN Esophageal and Esophagogastric Junction Cancers guidelines (4.2024) recommend HER2/*ERBB2* testing using FISH or IHC for patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma if trastuzumab is being considered for treatment. (p. ESOPH-B, 3 of 6)

NCCN Head and Neck Cancers guidelines (4.2024) recommend HER2/*ERBB2* testing prior to treatment for individuals diagnosed with recurrent, unresectable, or metastatic salivary gland tumors. (p. SALI-4)

NCCN Colon Cancer guidelines (4.2024) 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 (2.2024) recommend HER2/*ERBB2* testing for patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach if trastuzumab is being considered. (p. GAST-B, 3 of 6)

NCCN Breast Cancer guidelines (4.2024) 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 (3.2024) recommend HER2 testing for recurrent, advanced or metastatic cervical carcinoma. (p. CERV-A 1 of 7)

NCCN Uterine Neoplasms guidelines (2.2024) recommend HER2 IHC with reflex to FISH for all serous and carcinosarcoma endometrial tumors and recommends consideration of HER2 testing for all tumors that have abnormal p53 by IHC. (p. ENDO-A, 1 of 4)

NCCN guidelines for Pancreatic Adenocarcinoma (3.2024) indicate that testing for potentially actionable somatic findings including HER2 amplifications is recommended for patients with locally advanced or metastatic disease (p. PANC-5), recurrence after resection (p. PANC-9), and with resectable or borderline resectable disease being considered for neoadjuvant systemic therapy. (p. PANC-F, 1 of 12)

NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (3.2024) recommend HER2 testing by IHC for recurrent disease after primary treatment. (p. OV-6)

NCCN guidelines for Vaginal Cancer (1.2025) recommend consideration of HER2 testing by IHC or FISH for recurrent or metastatic vaginal cancer. (p. VAG-5, VAG-6, VAG-A 2 of 2)

NCCN guidelines for Bladder Cancer (4.2024) recommend consideration of IHC for HER2 overexpression for stage IIIB or higher muscle invasive bladder cancer. (p. BL-8-10)

NCCN guidelines for Small Bowel Adenocarcinoma (4.2024) recommend testing for HER2 amplifications for patients with metastatic disease. (p. SBA-5)

Multiple Myeloma FISH Panel Analysis

National Comprehensive Cancer Network (NCCN)
NCCN Multiple Myeloma guidelines (4.2024) 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 (3.2024) 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 including NTRK as part of disease workup. (p. ANAP-1, p. PAP-10, p. FOLL-9, p. ONC-9)

The NCCN Colon Cancer Guidelines (4.2024) recommend broad molecular profiling to identify rare and actionable mutations and fusions, including NTRK, for patients with suspected or proven metastatic adenocarcinoma. (p. COL-2) For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib. (p. COL-D 2 of 11)

The NCCN Non-Small Cell Lung Cancer guidelines (7.2024) recommends *NTRK* molecular analysis for patients with advanced or metastatic adenocarcinoma, large cell carcinoma, and NSCLC not otherwise specified (NOS) and recommends consideration of *NTRK* testing for advanced or metastatic squamous cell carcinoma of the lung. (p. NSCL-19) For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib. (p. NSCL-33)

The NCCN Occult Primary guidelines (1.2025) 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 entrectinib and/or larotrectinib or repotrectinib. (p. OCC-B, 2 of 11)

The NCCN Cervical Cancer guidelines (3.2024) recommends *NTRK* fusion analysis for patients with cervical sarcoma. (p. CERV-A 1 of 7)

The NCCN Vulvar Cancer guidelines (4.2024) recommends consideration of *NTRK* fusion analysis for recurrent, progressive, or metastatic squamous cell carcinoma of the vulva. (p. VULVA-A 2 of 4)
The NCCN Uterine Neoplasms guidelines (2.2024) recommends consideration of *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 (4.2024) recommend NTRK fusion testing for recurrent unresectable or stage IV disease if eligible for larotrectinib, entrectinib or repotrectinib treatment (no known resistance mutation and no satisfactory alternatives or have progressed on treatment). (p. BINV-Q 6 of 14)

The NCCN Gastric Cancer guidelines (2.2024) recommends consideration of comprehensive genomic profiling including *NTRK* fusion analysis for unresectable locally advanced, recurrent, or metastatic gastric cancer. (p. GAST-B 5 of 6)

The NCCN Esophageal and Esophagogastric Junction Cancer guidelines (4.2024) recommends consideration of comprehensive genomic profiling including *NTRK* fusion analysis for unresectable, locally advanced, recurrent, or metastatic esophageal cancer. (p. ESOPH-B 5 of 6) For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib. (p. ESOPH-F 6 of 22)

The NCCN Acute Lymphoblastic Leukemia guidelines (2.2024) and Pediatric Acute Lymphoblastic Leukemia guidelines (6.2024) recommend *NTRK* fusion analysis for acute lymphoblastic leukemia (ALL) for the purposes of risk stratification. (p. ALL-3; p. PEDALL-A 1 of 2)

The NCCN Soft Tissue Sarcoma guidelines (2.2024) recommend larotrectinib, entrectinib or repotrectinib for patients with advanced or metastatic disease and *NTRK* gene fusion-positive tumors. (p. SARC-G 1 of 13)

The NCCN Neuroendocrine and Adrenal Tumors guidelines (2.2024) recommends consideration of *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) For individuals who are *NTRK* gene fusion-positive, NCCN

lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib. (p. NE-H 5 of 9

The NCCN Head and Neck Cancers guidelines (4.2024) recommend 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 (2.2024) indicate that larotrectinib, entrectinib, and repotrectinib are options for treatment in patients with NTRK gene fusion positive tumors. (p. HCC-I, 1 of 2)

The NCCN Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer guidelines (3.2024) recommend tumor molecular testing including *NTRK* testing for recurrent disease if prior testing for these markers was not done. (p. OV-6) For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib. (p. OV-C 8 of 12)

The NCCN Small Bowel Adenocarcinoma guidelines (4.2024) recommends larotrectinib and entrectinib as options for subsequent-line treatment of metastatic small bowel adenocarcinoma that is *NTRK* gene fusion positive. (p. SBA-D 1 of 7)

The NCCN Pediatric Central Nervous System Cancers guidelines (1.2024) 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. PGLIO-B, 2 of 4)

The NCCN guidelines for Pancreatic Adenocarcinoma (3.2024) recommend testing for potentially actionable somatic findings including *NTRK* fusions for patients with locally advanced/metastatic disease. (p. PANC-1A) In addition, patients with resectable or borderline resectable disease who are considering systemic therapy are recommended to consider testing for somatic findings including NTRK fusions. (p. PANC-F, 1 of 12) For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib. (p. PANC-F 3 of 12)

The NCCN guidelines for Vaginal Cancer (1.2025) recommend consideration of NTRK fusion testing for recurrent or metastatic vaginal cancer. (p. VAG-5, VAG-6, VAG-A 2 of 2)

The NCCN guidelines for Gastrointestinal Stromal Tumors (2.2024) lists the following biomarker-directed therapies for individuals with unresectable, progressive or metastatic disease: entrectinib, larotrectinib, and repotrectinib. (p. GIST-E 1 of 4)

Food and Drug Administration
The FDA label for Augtyro (repotrectinib) includes indications and usage information for the treatment of the following:

- "adult patients with locally advanced or metastatic ROS1-positive nonsmall cell lung cancer (NSCLC). (1.1)
- adult and pediatric patients 12 years of age and older with solid tumors that:
  - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and
  - are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.
  - have progressed following treatment or have no satisfactory alternative therapy.

Tumor Specific PD-L1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN Gastric Cancer guidelines (2.2024) recommends PD-L1 testing during the workup for documented or suspected metastatic adenocarcinoma. (p. GAST-1)

The NCCN Head and Neck Cancers guidelines (4.2024) state recommendations for first line therapy which could include PD-L1 inhibitors for recurrent, unresectable, oligometastatic, or metastatic cancer of the nasopharynx. (p. NASO-B 1 of 3)

The NCCN Bladder Cancer guidelines (4.2024) states recommendations for specific therapies for individuals with locally advanced or metastatic (stage IV) bladder cancer, which can include PD-L1 inhibitors. (p. BL-G 2 of 7)

The NCCN Vulvar Cancer guidelines (4.2024) recommends consideration of PD-L1 testing for individuals with recurrent, progressive, or metastatic squamous cell carcinoma of the vulva. (p. VULVA-A 2 of 4)

The NCCN Esophageal and Esophagogastric Junction Cancers guidelines (4.2024) 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 (3.2024) 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 7)

NCCN Non-Small Cell Lung Cancer guidelines (7.2024) recommend PD-L1 testing in patients with stage IB-IIIA, IIIB [T3, N2] non-small cell lung cancer perioperatively (p. NSCL-E, 1 of 5) or for advanced or metastatic adenocarcinoma, large cell, squamous cell, and NSCLC not otherwise specified (NOS). (p. NSCL-19)

The NCCN Breast Cancer guidelines (4.2024) states recommendations for treatments for recurrent unresectable or stage IV triple negative breast cancer based on PD-L1 tumor status. (p. BINV-Q 2 of 14)

NCCN guidelines for Vaginal Cancer (1.2025) recommend consideration of PD-L1 testing for recurrent or metastatic vaginal cancer. (p. VAG-5, VAG-6, VAG-A 2 of 2).

Food and Drug Administration (FDA)

The FDA's list of cleared or approved companion diagnostic devices lists several cancer types approved for testing via the immunohistochemistry assay for PD-L1 for the purposes of treatment decision-making. These cancer types include, in part: head and neck squamous cell carcinoma, urothelial carcinoma (PMA number 150013, supplement number S014), and triple negative breast cancer (PMA number 150013, supplement S020).

Tumor Specific FOLR1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (3.2024) 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 12)

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 (3.2024) 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-1). 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-4)

Tumor Specific *RET* Gene Rearrangement Tests (FISH)
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Thyroid Carcinoma (3.2024) recommend that patients with recurrent or persistent medullary thyroid carcinoma have somatic *RET* testing if germline wild type or germline unknown (p. MEDU-6). The guideline also recommends that individuals with anaplastic thyroid cancer and/or locally recurrent, advanced and/or metastatic papillary, follicular, or oncocytic carcinoma that cannot be treated with radioactive iodine should undergo molecular testing including *BRAF*, *NTRK*, *ALK*, *RET* and tumor mutational burden if not previously done. (p. ANAP-3, PAP-10, FOLL-9, ONC-9)

The NCCN guideline on Non-Small Cell Lung Cancer (7.2024) recommends analysis for *RET* gene rearrangements in patients with advanced or metastatic adenocarcinoma of the lung, large cell carcinoma of the lung, or NSCLC not otherwise specified and recommends consideration of RET gene testing for patients with advanced or metastatic squamous cell carcinoma of the lung (p. NSCL-19), 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 8)

The NCCN guideline for Cervical Cancer (3.2024) recommends consideration of *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 7)

NCCN guidelines for Breast Cancer (4.2024) 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 (4.2024) recommend broad molecular profiling including *RET* fusion detection as part of the workup for suspected or proven metastatic adenocarcinoma. (p. COL-2)

NCCN guidelines for Pancreatic Adenocarcinoma (3.2024) recommends consideration of testing for potentially actionable somatic mutations including *RET* fusions for resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-F, 1 of 12) and recommends this testing for locally advanced/metastatic disease. (p. PANC-1A)

NCCN guidelines for Esophageal and Esophagogastric Junction Cancers (4.2024) recommend biomarker testing for patients with locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer and lists RET gene fusion as a targeted biomarker. (p. ESOPH-B, 5 of 6)

NCCN guidelines for Gastric Cancer (2.2024) recommend biomarker testing for patients with locally advanced, recurrent or metastatic gastric cancer and lists RET gene fusion as a targeted biomarker. (p. GAST-B, of 6)

NCCN guidelines for Vaginal Cancer (1.2025) recommend consideration of RET fusion testing for recurrent or metastatic vaginal cancer. (p. VAG-A 2 of 2)

Tumor Specific *ROS1* Gene Rearrangement
National Comprehensive Cancer Network (NCCN)
NCCN Non-Small Cell Lung Cancer guidelines (7.2024) recommend *ROS1* rearrangement testing in patients with advanced or metastatic disease of the following lung cancer pathologies: Adenocarcinoma, Large Cell, and NSCLC not otherwise specified (NOS) and recommends consideration of this testing for patients with squamous cell carcinoma of the lung. (p. NSCL-19)
NCCN guidelines for Ampullary Adenocarcinoma (2.2024) recommend consideration of tumor molecular profiling, including for ROS1 fusions, for patients with locally advanced or metastatic disease who are considering systemic therapy. (p. AMP-3)

NCCN guidelines for Pancreatic Adenocarcinoma (3.2024) recommends consideration of tumor molecular profiling including ROS1 fusions for patients with resectable or borderline resectable disease in advance of systemic therapy (p. PANC-F, 1 of 12) and recommends this testing for locally advanced or metastatic disease. (p. PANC-1A)

NCCN guidelines for Pediatric Central Nervous System Cancers (1.2024) state that broad molecular testing is required for comprehensive classification of pediatric diffuse high-grade gliomas, including detection of fusions involving *ROS1*. (p. PGLIO-B, 2 of 4)

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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.
01/01/2025	Annual review. Policy statement 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	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
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. **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:	**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 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 has hematuria, **AND**

POLICY STATEMENT	
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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.	1. Diagnostic studies have failed to identify the etiology of the hematuria, **AND** 2. A bladder cancer diagnostic and recurrence FISH test has not been ordered more than 1 time in the past 12 months, **OR** B. The member has been treated for bladder cancer, **AND** 1. The bladder cancer diagnostic and recurrence FISH tests are ordered with the following frequency: a. No more than 4 bladder tumor marker studies per year for years 1 to 2 after diagnosis b. No more than 3 bladder tumor marker studies per year during year 3 after diagnosis c. No more than 2 bladder tumor marker studies during year 4 after diagnosis d. 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**.	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.	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).	**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)	**Tumor Specific *ERBB2 (HER2)* Deletion/Duplication (FISH and CISH)**

POLICY STATEMENT	
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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.	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 to IV invasive breast cancer 2. Inoperable locally advanced, recurrent or metastatic gastric cancer 3. Suspected or proven metastatic colorectal cancer or appendiceal adenocarcinoma 4. Inoperable locally advanced, recurrent or metastatic esophageal and/or esophagogastric junction adenocarcinoma 5. Recurrent, unresectable, or metastatic salivary gland tumors, **OR** 6. Recurrent, advanced or metastatic cervical carcinoma 7. Serous endometrial carcinoma 8. Endometrial carcinosarcoma 9. p53 abnormal endometrial carcinoma 10. Resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma 11. Recurrent ovarian/fallopian tube/primary peritoneal cancer 12. Recurrent or metastatic vaginal cancer 13. Stage IIIB or higher muscle invasive bladder cancer 14. Metastatic small bowel adenocarcinoma.
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.	**Multiple Myeloma FISH Panel Analysis** VII. Multiple myeloma FISH panel analysis (88237, 88271, 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.

POLICY STATEMENT	
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***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	***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: 1. Advanced, progressive, or metastatic solid tumor, **OR** 2. Cancer for which surgical resection is not possible, **OR** 3. Unknown primary cancers, **OR** B. The member has a diagnosis of any of the following cancers at any stage: 1. Cervical sarcoma, **OR** 2. Anaplastic thyroid carcinoma, **OR** 3. Acute lymphoblastic leukemia (ALL), **OR** 4. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma.

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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.	**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 unresectable or stage IV triple negative breast cancer 8. Locally advanced, recurrent or metastatic esophageal and/or esophagogastric junction adenocarcinoma 9. Locally advanced, recurrent or metastatic gastric adenocarcinoma, **OR** 10. Recurrent, unresectable, oligometastatic, or metastatic nasopharyngeal cancer 11. Recurrent, progressive or metastatic squamous cell vulvar cancer 12. Recurrent or metastatic vaginal cancer.

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Note: PD-L1 protein expression analysis via IHC is often performed as an adjunct component of comprehensive molecular profiling panels for solid tumors	**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 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 *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**	**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: 1. Recurrent or persistent locoregional or metastatic medullary thyroid cancer, **AND** a. Germline testing for *RET* mutations is negative or has not been done, **OR** 2. Anaplastic thyroid carcinoma, **OR** 3. Locally recurrent, advanced and/or metastatic papillary thyroid carcinoma, **OR** 4. Locally recurrent, advanced and/or metastatic follicular thyroid carcinoma, **OR**

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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	5. Locally recurrent, advanced and/or metastatic oncocytic carcinoma (formerly called Hurthle cell carcinoma), **OR** 6. Advanced or metastatic adenocarcinoma of the lung, **OR** 7. Advanced or metastatic large cell cancer of the lung, **OR** 8. Advanced or metastatic non-small cell cancer of the lung, not otherwise specified, **OR** 9. Locally advanced or metastatic squamous cell carcinoma of the cervix, **OR** 10. Locally advanced or metastatic adenocarcinoma of the cervix, **OR** 11. Locally advanced or metastatic adenosquamous carcinoma of the cervix, **OR** 12. Recurrent unresectable or stage IV breast cancer, **OR** 13. Suspected or confirmed metastatic colon cancer, **OR** 14. Resectable, borderline resectable, locally advanced or metastatic pancreatic adenocarcinoma, **OR** 15. Locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer, **OR** 16. Locally advanced, recurrent or metastatic gastric cancer, **OR** 17. Recurrent or metastatic vaginal cancer.
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	**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: B. 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

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7. Pediatric (diagnosed age 18 years or younger) diffuse high-grade glioma.	7. Pediatric (diagnosed age 18 years or younger) diffuse high-grade glioma.