

<b>BSC_CON_2.11</b>	<b>Oncology: Cytogenetic Testing</b>		
<b>Original Policy Date:</b>	December 1, 2023	<b>Effective Date:</b>	December 1, 2023
<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 20

**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.

<a href="#">Policy Statement Locations</a>	Example Tests, Labs	Common CPT Codes
<a href="#">Tumor Specific ALK Gene Rearrangement (Qualitative FISH and PCR) Tests</a>	ALK Gene Rearrangements (Labcorp)	88271, 88274
<a href="#">Tumor Specific BCR/ABL Gene Rearrangement (Qualitative FISH and PCR) Tests</a>	Detection by FISH of t(9;22) BCR/ABL (CGC Genetics)	81479, 88271, 88274, 88275, 88291
	BCR/ABL t(9;22) (NeoGenomics Laboratories)	
	BCR ABL Qualitative (Cincinnati Children’s Hospital)	
<a href="#">Bladder Cancer Diagnostic and Recurrence FISH Tests</a>	UroVysion FISH (ARUP Laboratories)	88120, 88121
<a href="#">Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis</a>	FISH for Chronic Lymphocytic Leukemia (Cleveland Clinic Laboratories)	88271, 88274, 88275, 88291
	FISH, B-Cell Chronic Lymphocytic Leukemia Panel (Quest Diagnostics)	
<a href="#">Tumor Specific ERBB2 (HER2) Deletion/Duplication (FISH and CISH)</a>	ERBB2 (HER2/neu) Gene Amplification by FISH with Reflex, Tissue (ARUP Laboratories)	88360, 88377
<a href="#">Multiple Myeloma FISH Panel Analysis</a>	Oncology FISH Analysis - Multiple Myeloma FISH Panel (Baylor Genetics, LLC)	88271, 88237, 88275, 88291
	Multiple Myeloma (MM) FISH Profile (Labcorp)	
<a href="#">NTRK Fusion Analysis Panel</a>	NTRK NGS Fusion Panel (NeoGenomics Laboratories)	81191, 81192, 81193, 81194
<a href="#">Tumor Specific PD-L1 Protein Analysis</a>	PD-L1, IHC with Interpretation (Quest Diagnostics)	88341, 88342, 88360, 88361
<a href="#">Tumor Specific FOLR1 Protein Analysis</a>	FOLR1 Immunohistochemistry Analysis (Labcorp)	88360
<a href="#">Tumor Specific PML/RARA Gene Rearrangement (Qualitative FISH and PCR)</a>	FISH, AML M3, PML/RARA, Translocation 15, 17 (Quest Diagnostics)	81315, 81316, 88271, 88274, 88275, 88291
	PML/RARA - t(15;17) RT-PCR - Quantitative (Labcorp)	
<a href="#">Tumor Specific RET Gene</a>	RET FISH (NeoGenomics Laboratories)	88374, 88377, 88271,

<a href="#">Policy Statement Locations</a>	Example Tests, Labs	Common CPT Codes
<a href="#">Rearrangement (FISH)</a>	Oncology FISH Analysis - RET Rearrangement (Baylor Genetics)	88275, 88291
<a href="#">Tumor Specific <i>ROS1</i> Gene Rearrangement</a>	FISH <i>ROS1</i> 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

### 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, 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**.

### 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)

**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
    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.

**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.

***NTRK* Fusion Analysis Panel**

- VII. *NTRK1/2/3* 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 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

**Tumor Specific *PD-L1* Protein Analysis**

- 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

#### 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 *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
  - 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)

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

## Policy Guidelines

### Notes and Definitions

1. **Advanced cancer** is 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.

## 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. ***(to be published)***
- ***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

- N/A

## Rationale

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

*National Comprehensive Cancer Network (NCCN)*

The NCCN Thyroid Carcinoma guidelines (3.2023) 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 (3.2023) recommend *ALK* rearrangement testing in patients with Stage IB-III A, 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)

### Tumor Specific *BCR/ABL* Gene Rearrangement (Qualitative FISH and PCR) Tests

*National Comprehensive Cancer Network (NCCN)*

NCCN Acute Lymphoblastic Leukemia guidelines (2.2023) recommend *BCR/ABL* rearrangement analysis for patients for the diagnosis/workup of ALL. (p. ALL-1)

NCCN Acute Myeloid Leukemia guidelines (4.2023) recommend *BCR/ABL* rearrangement analysis for patients to stratify risk for AML. (p. AML-A 1 of 4)

NCCN Pediatric Acute Lymphoblastic Leukemia guidelines (2.2023) recommend *BCR/ABL* rearrangement analysis for patients for the diagnosis/work-up of ALL. (p. PEDALL-1)

NCCN Chronic Myeloid Leukemia guidelines (1.2024) recommend *BCR/ABL* rearrangement analysis for patients for the diagnosis/work-up of CML. (p. CML-1)

NCCN Myeloproliferative Neoplasms guidelines (1.2023) recommend *BCR/ABL* rearrangement analysis for patients during the workup of suspected MPN. (p. MPN-1)

NCCN B-cell Lymphoma guidelines (5.2023) include molecular testing PCR for *BCR-ABL* as one of the essential steps in diagnostic testing for lymphoblastic lymphoma. (p. BLAST-1)

### Bladder Cancer Diagnostic and Recurrence FISH Tests

*National Comprehensive Cancer Network (NCCN)*

NCCN Bladder Cancer guidelines (3.2023) 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) 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 (3.2023) 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 (2.2023) recommend *HER2/ERBB2* testing during the workup of documented or suspected metastatic adenocarcinoma. (p. ESOPH-1)

NCCN Head and Neck Cancers guidelines (2.2023) 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 (2.2023) recommend *HER2/ERBB2* testing during the workup for suspected or proven metastatic synchronous colorectal cancer (p. COL-4) or documented metachronous metastases by CT, MRI and/or biopsy. (p. COL-9)

NCCN Gastric Cancer guidelines (1.2023) recommend *HER2/ERBB2* testing for patients in the following clinical scenarios: locally advanced, recurrent, or metastatic adenocarcinoma of the stomach, for whom trastuzumab therapy (or FDA-approved equivalent medication) is being considered for treatment. (p. GAST-B 3 of 6).

NCCN Breast Cancer guidelines (4.2023) recommend *HER2/ERBB2* testing be performed on all patients with newly diagnosed primary or metastatic breast cancer. (p. BINV-A 1 of 2)

**Multiple Myeloma FISH Panel Analysis***National Comprehensive Cancer Network (NCCN)*

NCCN Multiple Myeloma guidelines (3.2023) 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 (3.2023) recommend that individuals with anaplastic thyroid cancer or locally recurrent, advanced, and/or metastatic papillary, follicular, and Hurthle cell 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. HURT-8).

The NCCN Colon Cancer guidelines (2.2023) recommends *NTRK* fusion analysis for patients with advanced or metastatic colorectal cancer. (p. COL-B 5 of 8).

The NCCN Non-Small Cell Lung Cancer guidelines (3.2023) recommends *NTRK* fusion analysis for patients with advanced or metastatic disease of lung Adenocarcinoma, Large Cell, Squamous cell carcinoma, and NSCLC not otherwise specified (NOS). (p. NSCL-18).

The NCCN Occult Primary guidelines (3.2023) recommends *NTRK* fusion analysis for cancer of unknown primary. (p. OCC-A 1 of 5).

The NCCN Cervical Cancer guidelines (1.2023) recommends *NTRK* fusion analysis for patients with cervical sarcoma. (p. CERV-A 1 of 3).

The NCCN Vulvar Cancer guidelines (1.2023) recommends *NTRK* fusion analysis for recurrent, progressive, or metastatic vulvar cancer. (p. VULVA-A 1 of 3).

The NCCN Uterine Neoplasms guidelines (2.2023) recommends *NTRK* fusion analysis for recurrent or metastatic endometrial carcinoma (p. ENDO-A 2 of 4) or a diagnosis of uterine sarcoma. (p. UTSARC-A 1 of 8).

The NCCN Breast Cancer guidelines (4.2023) recommends *NTRK* fusion analysis for recurrent unresectable or stage IV invasive breast cancer. (p. BINV-R 1 of 3)

The NCCN Gastric Cancer guidelines (1.2023) 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 (2.2023) 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 (2.2023) and Pediatric Acute Lymphoblastic Leukemia guidelines (2.2023) recommend *NTRK* fusion analysis for acute lymphoblastic leukemia (ALL). (p. ALL-A 1 of 2; p. PEDALL-A)

The NCCN Soft Tissue Sarcoma guidelines (1.2023) recommends *NTRK* fusion analysis for soft tissue sarcoma to guide medical management. (p. SARC-F 1 of 11)

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).

**Tumor Specific *PD-L1* Protein Analysis***National Comprehensive Cancer Network (NCCN)*

The NCCN Gastric Cancer guidelines (1.2023) recommends *PD-L1* testing during the workup for documented or suspected metastatic adenocarcinoma. (p. GAST-1)



The NCCN Head and Neck Cancers guidelines (2.2023) recommends *PD-L1* testing during the workup phase for recurrent, unresectable, oligometastatic, or metastatic cancer of the nasopharynx. (p. NASO-B 1 of 3)

NCCN Bladder Cancer guidelines (3.2023) 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 (1.2023) 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 (2.2023) 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 (1.2023) 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 (3.2023) recommend *PD-L1* testing in patients with stage IB-III A, 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 (4.2023) 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 (2.2023) 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 (4.2023) 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 (3.2023) 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 (3.2023) 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 (1.2023) 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)

### Tumor Specific *ROS1* Gene Rearrangement

*National Comprehensive Cancer Network (NCCN)*

NCCN Non-Small Cell Lung Cancer guidelines (3.2023) 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)

## References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2023.  
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2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2023.  
[http://www.nccn.org/professionals/physician\\_gls/PDF/colon.pdf](http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf)
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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., imaging, 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
	81479	Unlisted molecular pathology procedure
	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)	

Type	Code	Description
	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.

## 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](http://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](mailto: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	AFTER
<p><b>New Policy</b></p> <p><b>Policy Statement:</b> N/A</p>	<p><b>Oncology: Cytogenetic Testing BSC_CON_2.11</b></p> <p><b>Policy Statement:</b>  <b>Tumor Specific <i>ALK</i> Gene Rearrangement (Qualitative FISH and PCR) Tests</b></p> <ol style="list-style-type: none"> <li>I. Somatic <i>ALK</i> rearrangement analysis (88271, 88274) in solid tumors may be considered <b>medically necessary</b> when:             <ol style="list-style-type: none"> <li>A. The member has a diagnosis of or is in the initial work up stage for <b>any</b> of the following:                 <ol style="list-style-type: none"> <li>1. Stage IB or higher lung adenocarcinoma</li> <li>2. Stage IB or higher large cell lung carcinoma</li> <li>3. Stage IB or higher squamous cell lung carcinoma</li> <li>4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS)</li> <li>5. Anaplastic thyroid carcinoma</li> <li>6. Locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma</li> <li>7. Locally recurrent, advanced, and/or metastatic follicular thyroid cancer</li> </ol> </li> </ol> </li> <li>II. Tumor specific <i>BCR/ABL1</i> rearrangement analysis via fluorescent in situ hybridization (FISH) (88271, 88274, 88275, 88291) or PCR (81206, 81207, 81208, 81479) in peripheral blood or bone marrow may be considered <b>medically necessary</b> when the member meets <b>either</b> of the following:             <ol style="list-style-type: none"> <li>A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, or chronic myeloid leukemia)</li> <li>B. The member is undergoing diagnostic workup for <b>any</b> of the following:                 <ol style="list-style-type: none"> <li>1. Acute lymphoblastic leukemia (ALL)</li> <li>2. Acute myeloid leukemia (AML)</li> <li>3. Chronic myeloid leukemia (CML)</li> </ol> </li> </ol> </li> </ol> <p><b>Tumor Specific <i>BCR/ABL1</i> Gene Rearrangement (Qualitative FISH and PCR) Tests</b></p>

POLICY STATEMENT

BEFORE

AFTER

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**.

**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)

**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
    - 3. Suspected or proven metastatic colorectal cancer or documented metachronous metastases by CT, MRI, and/or biopsy



POLICY STATEMENT

BEFORE

AFTER

- 4. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma
- 5. Recurrent, unresectable, or metastatic salivary gland tumors.

**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.

**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
    - 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

**POLICY STATEMENT**

**BEFORE**

**AFTER**

- 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

**Tumor Specific PD-L1 Protein Analysis**

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

**POLICY STATEMENT**

**BEFORE**

**AFTER**

**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 *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

POLICY STATEMENT	
BEFORE	AFTER
	<p>H. The member has a diagnosis of advanced or metastatic non small-cell cancer of the lung, not otherwise specified</p> <p>I. The member has locally advanced or metastatic squamous cell carcinoma of the cervix</p> <p>J. The member has locally advanced or metastatic adenocarcinoma of the cervix</p> <p>K. The member has locally advanced or metastatic adenosquamous carcinoma of the cervix.</p> <p><b>Tumor Specific <i>ROS1</i> Gene Rearrangement</b></p> <p>XII. Somatic <i>ROS1</i> rearrangement analysis via fluorescent in situ hybridization (FISH) (88271, 88274) in solid tumors may be considered <b>medically necessary</b> when:</p> <p>A. The member has a diagnosis of <b>any</b> of the following:</p> <ol style="list-style-type: none"> <li>1. <a href="#">Advanced</a> or metastatic lung adenocarcinoma</li> <li>2. <a href="#">Advanced</a> or metastatic large cell lung carcinoma</li> <li>3. <a href="#">Advanced</a> or metastatic squamous cell lung carcinoma</li> <li>4. <a href="#">Advanced</a> or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS)</li> </ol>