CONCERT GENETICS ONCOLOGY: CYTOGENETIC TESTING

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Coding implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

OVERVIEW

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).

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only and may not support medical necessity. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis.

Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests	*ALK* Gene Rearrangements (Labcorp)	88271, 88274	C34, C73	1, 4
Tumor Specific BCR/ABL Gene Rearrangement (Qualitative FISH and PCR) Tests	Detection by FISH of t(9;22) BCR/ABL (CGC Genetics)	81479, 88271, 88274, 88275, 88291	C91.00-C91.02, C92.0-C92.12, D45, D47.1, D47.3, D69.3	7, 8, 9, 10, 11, 24
	BCR/ABL t(9;22) (NeoGenomics Laboratories)			
	BCR ABL Qualitative (Cincinnati Children's Hospital)			
Bladder Cancer Diagnostic and Recurrence FISH Tests	UroVysion FISH (ARUP Laboratories)	88120, 88121	C67, D09.0, D49.4, R31.9, Z85.51	16, 18
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis	FISH for Chronic Lymphocytic Leukemia (Cleveland Clinic Laboratories)	88271, 88274, 88275, 88291	C91, C94, C95, Z85.6	12
	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	C08, C15, C16, C18, C19, C20, C50	2, 5, 6, 13, 14
Multiple Myeloma FISH Panel Analysis	Oncology FISH Analysis - Multiple Myeloma FISH Panel (Baylor Genetics, LLC)	88271, 88237, 88275, 88291	C90	15
	Multiple Myeloma (MM) FISH Profile (Labcorp)			
NTRK Fusion Analysis Panel	NTRK NGS Fusion Panel (NeoGenomics Laboratories)	81191, 81192, 81193, 81194	C15, C16, C18, C34,	1, 2, 3, 4, 5, 6,

			C49.9, C50, C51, C53, C54, C73, C80.1, C91	10, 11, 13, 17, 19, 20, 21, 22
Tumor Specific *PD-L1* Protein Analysis	PD-L1, IHC with Interpretation (Quest Diagnostics)	88341, 88342, 88360, 88361	C11, C15, C16, C34, C50, C51, C53, C67	1, 3, 5, 6, 13, 14, 16, 17
Tumor Specific FOLR1 Protein Analysis	FOLR1 Immunohistochemistry Analysis (Labcorp)	88360	C56	23
Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR)	FISH, AML M3, PML/RARA, Translocation 15, 17 (Quest Diagnostics) PML/RARA - t(15;17) RT-PCR - Quantitative (Labcorp)	81315*, 81316*, 88271, 88274, 88275, 88291	C91-C95	7
Tumor Specific *RET* Gene Rearrangement (FISH)	RET FISH (NeoGenomics Laboratories) Oncology FISH Analysis - RET Rearrangement (Baylor Genetics)	88374, 88377, 88271, 88275, 88291	C34, C53, C73	1, 3, 4
Tumor Specific *ROS1* Gene Rearrangement	FISH ROS1 Rearrangement (Johns Hopkins Medical Institutions-Pathology Laboratory)	88271, 88274	C34	1

OTHER RELATED POLICIES

This policy document provides 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 criteria related to genetic testing for hereditary cancer predisposition syndromes.
- ***Oncology: Cancer Screening*** for 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 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 criteria related to whole genome and whole exome sequencing in rare genetic syndromes.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to cytogenetic testing in oncology that is not specifically discussed in this or another non-general policy.

CRITERIA

It is the policy of Louisiana Healthcare Connections that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

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/enrollee has a diagnosis of or is in the initial work up stage for:

1. Stage IB or higher lung adenocarcinoma, **OR**
2. Stage IB or higher large cell lung carcinoma, **OR**
3. Stage IB or higher squamous cell lung carcinoma, **OR**
4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**
5. Anaplastic thyroid carcinoma, **OR**
6. Locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma, **OR**
7. Locally recurrent, advanced, and/or metastatic follicular thyroid cancer.

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Tumor Specific *BCR/ABL1* Gene Rearrangement (Qualitative FISH and PCR) Tests

I. Tumor specific *BCR/ABL1* rearrangement analysis via fluorescent in situ hybridization (FISH) (88271, 88274, 88275, 88291) or PCR (81479) in peripheral blood or bone marrow is considered **medically necessary** when:

   A. The member/enrollee is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, or chronic myeloid leukemia), **OR**

   B. The member/enrollee is undergoing diagnostic workup for:

      1. Acute lymphoblastic leukemia (ALL), **OR**
      2. Acute myeloid leukemia (AML), **OR**
      3. Chronic myeloid leukemia (CML), **OR**
      4. B-cell lymphoma.

Note: Refer to *Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies* for criteria regarding minimal residual disease (MRD) indications for *BCR/ABL1* to monitor disease progression.

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Bladder Cancer Diagnostic and Recurrence FISH Tests

I. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for screening, diagnosing, and monitoring bladder cancer are considered **investigational**.

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

I. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) FISH panel analysis (88271, 88274, 88275, 88291) in peripheral blood or bone marrow is considered **medically necessary** when:

   A. The panel includes analysis for +12, del(11q), del(13q), and del(17p), **AND**

   B. The member/enrollee is undergoing initial diagnostic workup for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

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

I. Somatic *ERBB2 (HER2*) amplification analysis via in situ hybridization (ISH) (i.e., FISH or CISH) or immunohistochemistry (IHC) (88360, 88377) in solid tumors is considered **medically necessary** when:

A. The member/enrollee has any of the following:

1. Recurrent or newly diagnosed stage I-IV invasive breast cancer, **OR**
2. Inoperable locally advanced, recurrent, or metastatic gastric cancer and trastuzumab (or FDA-approved equivalent medication) is being considered for treatment, **OR**
3. Suspected or proven metastatic colorectal cancer or documented metachronous metastases by CT, MRI, and/or biopsy, **OR**
4. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma, **OR**
5. Recurrent, unresectable, or metastatic salivary gland tumors.

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Multiple Myeloma FISH Panel Analysis

I. Multiple myeloma FISH panel analysis (88271, 88273, 88275, 88291) of bone marrow is considered **medically necessary** when:

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), **AND**

B. The member/enrollee is undergoing initial diagnostic workup for multiple myeloma.

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NTRK Fusion Analysis Panel

I. *NTRK 1/2/3* fusion analysis panel (81191, 81192, 81193, 81194) via fluorescent in situ hybridization (FISH) or immunohistochemistry (IHC) in solid tumors is considered **medically necessary** when:

A. The member/enrollee is undergoing initial diagnostic workup for or has a diagnosis of:

1. Advanced or metastatic lung adenocarcinoma, **OR**
2. Advanced or metastatic large cell lung carcinoma, **OR**
3. Advanced or metastatic squamous cell lung carcinoma, **OR**
4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**
5. Unknown primary cancers, **OR**
6. Advanced or metastatic colorectal cancer, **OR**
7. Cervical sarcoma, **OR**
8. Recurrent, progressive, or metastatic vulvar cancer, **OR**
9. Recurrent or metastatic endometrial carcinoma or a diagnosis of uterine sarcoma, **OR**
10. Recurrent unresectable or stage IV invasive breast cancer, **OR**
11. Unresectable locally advanced, recurrent, or metastatic gastric cancer, **OR**
12. Unresectable locally advanced, recurrent, or metastatic esophageal cancer, **OR**
13. Anaplastic thyroid carcinoma or locally recurrent, advanced, and/or metastatic papillary, follicular, or Hurthle cell thyroid carcinoma, **OR**
14. Acute lymphoblastic leukemia (ALL), **OR**
15. Soft tissue sarcoma, **OR**
16. Unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm.

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Tumor Specific *PD-L1* Protein Analysis

I. *PD-L1* protein expression analysis via immunohistochemistry (IHC) (88341, 88342, 88360, 88361) in solid tumors is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of or is in the initial work up stage for:

1. Stage IB or higher lung adenocarcinoma, **OR**
2. Stage IB or higher large cell lung carcinoma, **OR**
3. Stage IB or higher squamous cell lung carcinoma, **OR**
4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**
5. Locally advanced or metastatic bladder cancer, **OR**
6. Recurrent, progressive, or metastatic cervical cancer (squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma), **OR**
7. Recurrent or stage IV triple negative breast cancer, **OR**
8. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma, **OR**
9. Suspected or proven metastatic gastric adenocarcinoma, **OR**
10. Recurrent, unresectable, oligometastatic, or metastatic nasopharyngeal cancer, **OR**
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

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Tumor Specific FOLR1 Protein Analysis

I. Tumor specific FOLR1 protein expression analysis via immunohistochemistry (IHC) analysis (88360) is considered medically necessary when:

A. The member/enrollee has a diagnosis of epithelial ovarian, fallopian tube or primary peritoneal cancer, **AND**
B. Elahere (mirvetuximab soravtansine) is being considered for treatment.

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

I. *PML/RARA* rearrangement analysis via fluorescent in situ hybridization (FISH) (81315*, 81316*, 88271, 88274, 88275, 88291) in peripheral blood or bone marrow is considered **medically necessary** when:

A. The member/enrollee is undergoing initial diagnostic work up for acute myeloid leukemia (AML).

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Tumor Specific RET Gene Rearrangement Tests (FISH)

I. Tumor specific *RET* gene rearrangement testing (88374, 88377, 88271, 88275, 88291) in solid tumors is considered **medically necessary** when:

A. The member/enrollee 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, **OR**

B. The member/enrollee has a diagnosis of anaplastic thyroid carcinoma, **OR**

C. The member/enrollee has or locally recurrent, advanced and/or metastatic papillary thyroid carcinoma, **OR**

D. The member/enrollee has locally recurrent, advanced and/or metastatic follicular thyroid carcinoma, **OR**

E. The member/enrollee has locally recurrent, advanced and/or metastatic Hurthle cell thyroid carcinoma, **OR**

F. The member/enrollee has a diagnosis of advanced or metastatic adenocarcinoma of the lung, **OR**

G. The member/enrollee has a diagnosis of advanced or metastatic large cell cancer of the lung, **OR**

H. The member/enrollee has a diagnosis of advanced or metastatic non small-cell cancer of the lung, not otherwise specified, **OR**

I. The member/enrollee has locally advanced or metastatic squamous cell carcinoma of the cervix, **OR**,

J. The member/enrollee has locally advanced or metastatic adenocarcinoma of the cervix, **OR**

K. The member/enrollee has locally advanced or metastatic adenosquamous carcinoma of the cervix.

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Tumor Specific *ROS1* Gene Rearrangement

I. Somatic *ROS1* rearrangement analysis via fluorescent in situ hybridization (FISH) (88271, 88274) in solid tumors is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of:

1. Advanced or metastatic lung adenocarcinoma, **OR**
2. Advanced or metastatic large cell lung carcinoma, **OR**
3. Advanced or metastatic squamous cell lung carcinoma, **OR**
4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

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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.

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BACKGROUND AND 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-IIIA, IIIB, disease perioperatively for consideration of systemic therapy(p. NSCL-E, 1 of 3) as well as for patients with advanced or metastatic Adenocarcinoma, Large Cell, Squamous cell, or NSCLC not otherwise specified (NOS). (p. NSCL-18)

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-IIIA, IIIB non-small cell lung cancer perioperatively (p. NSCL-E, 1 of 3) or for advanced or metastatic adenocarcinoma, large cell, squamous cell, and NSCLC not otherwise specified (NOS). (p. NSCL-18)

The NCCN Breast Cancer guidelines (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)

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Converted corporate to local policy.	09/23	11/27/23
Semi-annual review. Overview, coding, reference-table, background and references updated. Throughout policy: replaced “coverage criteria” with “criteria. For Overview: removed “also to”. For Policy Reference Table: removed “88275, 88291”; added Tumor Specific RET Gene Rearrangement (FISH) and related content. For Other Related Policies: added “and Molecular”. For Criteria; under Tumor Specific ALK Gene Rearrangement (Qualitative FISH and PCR) Tests: I. removed “88275, 88291”; I.A.1-I.A.4. replaced “Advanced or metastatic” with “Stage IB or higher”; I.A.5. added “OR”; I.A.6. added “Locally recurrent, advanced, and/or metastatic papillary…”; I.A.7. added “Locally recurrent, advanced, and/or metastatic follicular…”; under Tumor Specific BCR/ABL1 Gene Rearrangement (Qualitative FISH and PCR) Tests: I. replaced “Somatic” with “Tumor specific”; I.B.3. replaced “myelogenous” with “myeloid”; added “OR”; I.B.4. added “B-cell lymphoma”; added “Note: Refer to Oncology…”; under Tumor Specific ERBB2 (HER2) Deletion/Duplication (FISH and CISH): I. added “or immunohistochemistry (IHC)”; I.A.3. removed “synchronous”; under Multiple Myeloma FISH Panel Analysis: removed “88274”; added “88273”; for NTRK Fusion Analysis Panel: removed “Somatic”; added “panel”; added I.A.16. “Unresectable or metastatic…”; under Tumor Specific PD-L1 Protein Analysis: I.A.1-I.A.4. replaced “Advanced or metastatic” with “Stage IB or higher”; added Tumor Specific FOLR1 Protein Analysis	12/23	2/27/24

Reviews, Revisions, and Approvals	Revision Date	Approval Date
and related criteria; under Tumor Specific PML/RARA Gene Rearrangement (Qualitative FISH and PCR): I. added "81315, 81316"; added Tumor Specific RET Gene Rearrangement Tests (FISH) and related criteria. For Background and Rationale: added "ALK testing is also recommended…"; removed "advanced or metastatic disease of lung"; added "Stage IB-IIIA…"; added "NCCN B-cell Lymphoma…"; added "The NCCN Neuroendocrine…"; under Tumor Specific PD-L1 Protein Analysis: removed "advanced or metastatic disease…"; added "stage IB-IIIB…"; added Tumor Specific FOLR1 Protein Analysis and related content; added Tumor Specific *RET* Gene Rearrangement (FISH) and related content.		

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. LHCC retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom LHCC has no control or right of control. Providers are not agents or employees of LHCC.