CONCERT GENETICS ONCOLOGY: CYTOGENETIC TESTING

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Revision Log

Coding implications

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~~2023, 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.

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding 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.

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. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.

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, 22, 23, 24, 27
Bladder Cancer Diagnostic and Recurrence FISH Tests	UroVysion FISH (ARUP Laboratories)	88120, 88121	C67, D09.0, D49.4, R31.9, Z85.51	14, 16
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	10

~~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)~~ 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, 3, 5, 6, ~~13, 14~~11, 12, 18, 21, 22
~~Multiple Myeloma FISH Panel Analysis~~Multiple Myeloma FISH Panel Analysis	Oncology FISH Analysis - Multiple Myeloma FISH Panel (Baylor Genetics, LLC)	88271, 88237, 88275, 88291	C90	~~15~~13
	Multiple Myeloma (MM) FISH Profile (Labcorp)			
~~*NTRK* Fusion Analysis Panel~~*NTRK* Fusion Analysis Panel	NTRK NGS Fusion Panel (NeoGenomics Laboratories)	81191, 81192, 81193, 81194	C15, C16, C18, C34, C49.9, C50, C51, C53, C54, C73, C80.1, C91	1, 2, 3, 4, 5, 6, ~~10~~8, 9, 11, ~~13~~12, 15, 17, 18, 19, 20, 21, 22, 24, 25, 26
~~Tumor Specific *PD-L1* Protein Analysis~~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~~11, 12, 14, ~~16, 17~~15

~~Tumor Specific FOLR1 Protein Analysis~~ Tumor Specific FOLR1 Protein Analysis	FOLR1 Immunohistochemistry Analysis (Labcorp)	88360	C56	~~23~~21
~~Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR)~~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~~ (NeoGenomics Laboratories)	81315*, 81316*, 88271, 88274, 88275, 88291	C91-C95	7
~~Tumor Specific *RET* Gene Rearrangement (FISH)~~ 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, 2, 3, 4, 11, 22
~~Tumor Specific *ROS1* Gene Rearrangement~~ Tumor Specific *ROS1* Gene Rearrangement	FISH ROS1 Rearrangement (Johns Hopkins Medical Institutions-Pathology Laboratory)	88271, 88274	C34	1, 22, 23, 24

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.

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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~~.~~, **OR**

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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**~~

~~A. The member/enrollee is undergoing diagnostic workup for:~~

~~7.~~1. ~~Acute lymphoblastic leukemia (ALL), **OR**~~

~~8. Acute myeloid leukemia (AML), **OR**~~

~~9. Chronic myeloid leukemia (CML), **OR**~~

8. ~~B.~~ Locally advanced/metastatic ampullary adenocarcinoma, **OR**

~~1.~~9. Langerhans cell ~~lymphoma.~~histiocytosis, **OR**

~~**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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10. Erdheim-Chester disease, **OR**

11. Resectable, borderline resectable or locally advanced or metastatic pancreatic adenocarcinoma, **OR**

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

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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) (88377) 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~~Suspected or documented 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~~appendiceal adenocarcinoma, **OR**
4. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma, **OR**
5. Recurrent, unresectable, or metastatic salivary gland tumors~~.~~**, OR**

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6. Recurrent, advanced or metastatic cervical carcinoma, **OR**
7. Serous endometrial carcinoma, **OR**
8. Uterine carcinosarcoma, **OR**

9. Resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma, **OR**

10. Recurrent ovarian/fallopian tube/primary peritoneal cancer.

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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~~Advanced or metastatic lung adenocarcinoma, **OR**

2. ~~Advanced~~Advanced or metastatic large cell lung carcinoma, **OR**

3. ~~Advanced~~Advanced or metastatic squamous cell lung carcinoma, **OR**

4. ~~Advanced~~Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**

5. Unknown primary cancers, **OR**

6. ~~Advanced~~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~~, **OR**

~~9.~~10. Metastatic uterine sarcoma, **OR**

~~10.~~11. Recurrent unresectable or stage IV invasive breast cancer, **OR**

~~11.~~12. Unresectable locally advanced, recurrent, or metastatic gastric cancer, **OR**

~~12.~~13. Unresectable locally ~~advanced~~advanced, recurrent, or metastatic esophageal cancer, **OR**

~~13.~~14. Anaplastic thyroid carcinoma or locally recurrent, ~~advanced~~advanced, and/or metastatic papillary, follicular, or oncocytic carcinoma (formerly called Hurthle cell ~~thyroid~~ carcinoma~~,~~), **OR**

~~2. Acute lymphoblastic leukemia (ALL), **OR**~~

15. ~~Soft~~Acute lymphoblastic leukemia (ALL), **OR**

~~14.~~16. Advanced or metastatic soft tissue sarcoma, **OR**

~~15.~~17. Unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm~~.~~, **OR**

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18. Metastatic salivary gland tumors, **OR**

19. Unresectable or metastatic hepatocellular carcinoma, **OR**

20. Recurrent epithelial ovarian/Fallopian tube/primary peritoneal cancer, **OR**

21. Metastatic small bowel adenocarcinoma, **OR**

22. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma, **OR**

23. Resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma.

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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~~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~~**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~~recurrent, platinum resistant 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 via fluorescent in situ hybridization (FISH) (88374, 88377, 88271, 88275, 88291) in solid tumors is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of:

1. ~~The member/enrollee has a diagnosis of recurrent~~Recurrent or persistent locoregional or metastatic medullary thyroid cancer ~~and germline~~, **AND**

~~A.~~a) Germline testing for *RET* mutations is negative or has not been done, **OR**

~~B.~~2. ~~The member/enrollee has a diagnosis of anaplastic~~Anaplastic thyroid carcinoma, **OR**

~~C.~~3. ~~The member/enrollee has or locally~~Locally recurrent, advanced and/or metastatic papillary thyroid carcinoma, **OR**

~~D.~~4. ~~The member/enrollee has locally~~Locally recurrent, advanced and/or metastatic follicular thyroid carcinoma, **OR**

~~E.~~5. ~~The member/enrollee has locally~~Locally recurrent, advanced and/or metastatic oncocytic carcinoma (formerly called Hurthle cell ~~thyroid~~ carcinoma~~,~~), **OR**

F.6. The member/enrollee has a diagnosis of advancedAdvanced or metastatic adenocarcinoma of the lung, **OR**

G.7. The member/enrollee has a diagnosis of advancedAdvanced or metastatic large cell cancer of the lung, **OR**

H.8. The member/enrollee has a diagnosis of advancedAdvanced or metastatic non small-cell cancer of the lung, not otherwise specified, **OR**

I.9. The member/enrollee has locallyLocally advanced or metastatic squamous cell carcinoma of the cervix, **OR**,

J.10. The member/enrollee has locallyLocally advanced or metastatic adenocarcinoma of the cervix, **OR**

K.11. The member/enrollee has locallyLocally advanced or metastatic adenosquamous carcinoma of the cervix., **OR**

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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

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Tumor Specific *ROS1* Gene Rearrangement

I. SomaticTumor specific *ROS1* gene 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:

A. AdvancedThe member/enrollee has a diagnosis of:

1. Advanced or metastatic lung adenocarcinoma, **OR**
2. AdvancedAdvanced or metastatic large cell lung carcinoma, **OR**
3. AdvancedAdvanced or metastatic squamous cell lung carcinoma, **OR**

4. ~~Advanced~~Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS~~).~~), **OR**

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5. ~~NOTES AND~~ Locally advanced or metastatic ampullary adenocarcinoma, **OR**
6. Resectable or borderline resectable, or locally advanced or metastatic pancreatic adenocarcinoma, **OR**
7. Pediatric (diagnosed age 18 years or younger) diffuse high-grade glioma.

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DEFINITIONS

1. **Advanced cancer** ~~is 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.

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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~~4.2023) recommend that individuals with anaplastic thyroid cancer should undergo molecular testing including *BRAF*, *NTRK*, *ALK*, *RET*, MSI, dMMR, and tumor mutational burden if not previously done (p. ANAP-1). *ALK* testing is also recommended for locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma (p. PAP-10) and locally recurrent, advanced, and/or metastatic follicular thyroid carcinoma (p. FOLL-9).

NCCN Non-Small Cell Lung Cancer guidelines (~~3.2023~~2.2024) recommend *ALK* rearrangement testing in patients with Stage IB-IIIA, IIIB, disease perioperatively for consideration of systemic therapy (p. NSCL-E, 1 of 3) as well as for patients with advanced or metastatic ~~Adenocarcinoma,~~

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

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

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

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

~~. (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~~1.2024) do not currently mention a recommendation for the use of bladder cancer diagnostic and recurrence FISH tests. (e.g., Urovysion)

American Urological Association and Society of Urologic Oncology

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

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

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

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

National Comprehensive Cancer Network (NCCN)

NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guidelines (~~3.2023~~1.2024) recommend FISH testing for the rearrangements specified (at a minimum) during

the diagnostic workup for CLL/SLL, including: +12, del(11q), del(13q), and del(17p). (p. CSLL-1)

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

National Comprehensive Cancer Network (NCCN)

NCCN Esophageal and Esophagogastric Junction Cancers guidelines (~~2~~4.2023) recommend HER2/*ERBB2* testing during the workup of documented or suspected metastatic adenocarcinoma. (p. ESOPH-1)

NCCN Head and Neck Cancers guidelines (2.~~2023~~2024) recommend HER2/*ERBB2* testing for therapeutic options for individuals diagnosed with recurrent, unresectable, or metastatic salivary gland tumors. (p. SALI-B 1 of 2)

NCCN Colon Cancer guidelines (~~2.2023~~1.2024) 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.~~2) These guidelines also recommend HER2 analysis for metastatic appendiceal adenocarcinoma. (p. COL-~~9)~~I 2 of 3)

NCCN Gastric Cancer guidelines (~~1~~3.2023) 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.~~with suspected or documented metastatic disease. (p. GAST-~~B 3 of 6).~~1)

NCCN Breast Cancer guidelines (~~4.2023~~1.2024) recommend HER2/*ERBB2* testing be performed on all patients with newly diagnosed primary or metastatic breast cancer. (p. BINV-A 1 of 2)

NCCN Cervical Cancer guidelines (1.2024) recommend HER2 testing for recurrent, advanced or metastatic cervical carcinoma. (p. CERV-A 1 of 7)

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

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

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

Multiple Myeloma FISH Panel Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Multiple Myeloma guidelines (~~3.2023~~2.2024) recommend FISH testing during the initial workup of multiple myeloma for prognostic purposes. The recommended FISH testing includes: del(13), del (17p13), t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/1q21 amplification, 1p deletion. (p. MYEL-1)

NTRK Fusion Analysis Panel

National Comprehensive Cancer Network (NCCN)

The NCCN Thyroid Carcinoma guidelines (~~3~~4.2023) recommend that individuals with anaplastic thyroid cancer or locally recurrent, advanced, and/or metastatic papillary, follicular, and ~~Hurthle cell~~oncocytic carcinoma (formerly called Hurthle cell carcinoma) undergo molecular testing as part of disease workup. Oncocytic carcinoma should undergo molecular testing including *BRAF*, *NTRK*, *ALK*, *RET*, MSI, dMMR, and tumor mutational burden if not previously done. (p. ANAP-1, p. PAP-9, p. FOLL-8, p. ~~HURT-8~~ONC-9)

The NCCN Colon Cancer ~~guidelines (~~Guidelines (1.2024) state that studies have estimated that about 0.2~~.2023 recommends~~% to 1% of CRCs carry *NTRK* ~~fusion analysis~~gene fusions. Two targeted therapies, larotrectinib and entrectinib, have been FDA-approved for the treatment of patients with ~~advanced or~~ metastatic ~~colorectal cancer.~~, unresectable solid tumors that have an *NTRK* gene fusion and no satisfactory alternative treatment options, regardless of the location of the primary tumor. (p. ~~COL-B 5 of 8)~~MS-70)

The NCCN Non-Small Cell Lung Cancer guidelines (~~3.2023~~2.2024) recommends *NTRK* fusion analysis for patients with advanced or metastatic ~~disease of lung Adenocarcinoma, Large Cell, Squamous~~adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and NSCLC not otherwise specified (NOS). (p. NSCL-18)

The NCCN Occult Primary guidelines (~~3.2023) recommends~~1.2024) states that patients with metastatic or unresectable *NTRK* gene fusion ~~analysis for cancer of unknown primary.~~positive adenocarcinomas without a known acquired resistance mutation, who have no satisfactory treatment options or who have progressed on treatment can be treated with larotrectinib (p. OCC-~~A 1~~B, 2 of ~~5)~~11).

The NCCN Cervical Cancer guidelines (1.~~2023~~2024) recommends *NTRK* fusion analysis for patients with cervical sarcoma. (p. CERV-A 1 of ~~3~~7).

The NCCN Vulvar Cancer guidelines (~~1.2023~~3.2024) 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~~1.2024) advises to consider *NTRK* fusion analysis for recurrent or metastatic endometrial carcinoma (p. ENDO-A 2 of 4) or ~~a diagnosis of~~metastatic uterine sarcoma. (p. UTSARC-A 1 of 8)

The NCCN Breast Cancer guidelines (~~4.2023) recommends~~1.2024) indicate that patients whose tumors have an *NTRK* gene fusion ~~analysis for recurrent unresectable~~without a known acquired resistance mutation and have no other satisfactory treatment options or ~~stage IV invasive breast cancer.~~have progressed following treatment can receive larotrectinib or entrectinib (p. BINV-~~R 1~~Q, 6 of ~~3)~~14).

The NCCN Gastric Cancer guidelines (~~1~~3.2023) recommends *NTRK* fusion analysis for unresectable locally advanced, recurrent, or metastatic gastric cancer. (p. GAST-B 5 of 6, p. GAST-F 4 of 16)

The NCCN Esophageal and Esophagogastric Junction Cancer guidelines (~~2~~4.2023) recommends *NTRK* fusion analysis for unresectable, locally advanced, recurrent, or metastatic esophageal cancer. (p. ESOPH-B 5 of 6, p. ESOPH-F 4 of 17)

The NCCN Acute Lymphoblastic Leukemia guidelines (~~2~~3.2023) and Pediatric Acute Lymphoblastic Leukemia guidelines (~~2.2023~~3.2024) recommend *NTRK* fusion analysis for acute lymphoblastic leukemia (ALL). (p. ALL-A 1 of 2; p. PEDALL-A)

The NCCN Soft Tissue Sarcoma guidelines (~~1.2023) recommends *NTRK* fusion analysis for soft tissue sarcoma to guide medical management. (p. SARC-F 1 of 11)~~3.2023) state that larotrectinib and entrectinib have demonstrated efficacy in patients with *NTRK* positive tumors and are recommended as first line treatment options for patients with advanced or metastatic *NTRK* positive sarcomas. (p. MS-29)

The NCCN Neuroendocrine and Adrenal Tumors guidelines (1.2023) recommends *NTRK* fusion testing for patients with unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm. (p. PDNEC-1~~).~~)

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

The NCCN Hepatocellular Carcinoma guidelines (2.2023) indicate that *NTRK1/NTRK2/NTRK3* fusions have not been reported in HCC. However, as studies have demonstrated response rates in the 57% to 75% range in pre-treated *NTRK* fusion-positive tumors, larotrectinib and entrectinib are subsequent-line systemic therapy options for patients with HCC that is *NTRK* gene fusion positive. (p. MS-37).

The NCCN Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer guidelines (1.2024) recommend tumor molecular testing including *NTRK* testing for recurrent disease if prior testing did not include these markers (p. OV-6)

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

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

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

Tumor Specific PD-L1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN Gastric Cancer guidelines (~~1~~3.2023) recommends PD-L1 testing during the workup for documented or suspected metastatic adenocarcinoma. (p. GAST-1)

The NCCN Head and Neck Cancers guidelines (2.~~2023~~2024) recommends PD-L1 testing during the workup phase for recurrent, unresectable, oligometastatic, or metastatic cancer of the nasopharynx. (p. NASO-B 1 of 3)

The NCCN Bladder Cancer guidelines (~~3.2023~~1.2024) recommend PD-L1 testing in individuals with locally advanced or metastatic (stage IV) bladder cancer to guide medical management. (p. BL-G 2 of 7)

The NCCN Vulvar Cancer guidelines (~~1.2023~~3.2024) recommends PD-L1 testing for individuals with recurrent, progressive, or metastatic vulvar cancer. (p. VULVA-A 1 of 3)

The NCCN Esophageal and Esophagogastric Junction Cancers guidelines (~~2~~4.2023) recommends PD-L1 testing for individuals during the workup phase for documented or suspected metastatic esophageal and esophagogastric junction cancers. (p. ESOPH-1)

The NCCN Cervical Cancer guidelines (1.~~2023~~2024) recommends PD-L1 testing for individuals with recurrent, progressive, or metastatic cervical cancer of the following pathologies: squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. (p. CERV-A 1 of 3)

NCCN Non-Small Cell Lung Cancer guidelines (~~3.2023~~2.2024) recommend PD-L1 testing in patients with stage IB-IIIA, IIIB non-small cell lung cancer perioperatively (p. NSCL-E, 1 of 3) or for advanced or metastatic adenocarcinoma, large cell, squamous cell, and NSCLC not otherwise specified (NOS). (p. NSCL-18)

The NCCN Breast Cancer guidelines (~~4.2023~~1.2024) recommends PD-L1 testing for individuals with recurrent or stage IV triple negative breast cancer. (p. BINV-R 1 of 3)

Tumor Specific FOLR1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (~~2.2023~~1.2024) indicate that the preferred treatment regimen for platinum resistant recurrent disease includes mirvetuximab soravtansine if the tumor expresses folate receptor alpha (i.e., FOLR1). Therefore, tumor molecular analysis for this cancer type is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit, including folate receptor alpha (FOLR1) (p. OV-C, 9 and 10 of 11).

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

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

National Comprehensive Cancer Network (NCCN)

NCCN Acute Myeloid Leukemia guidelines (~~4~~6.2023) state that many different types of gene mutations are associated with specific prognoses, helping to guide medical management decisions, and/or may indicate that specific therapeutic agents are useful. Therefore, all patients with AML should be tested for these mutations. (p. EVAL-1A). The discussion section of this guideline states that *PML-RAR* alpha is included in this group of genetic markers that should be tested in all patients. (p. MS-3)

Tumor Specific *RET* Gene Rearrangement (FISH)

National Comprehensive Cancer Network (NCCN)

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

The NCCN guideline on Non-Small Cell Lung Cancer (~~3.2023~~2.2024) recommends analysis for *RET* gene rearrangements, noting that NGS-based methodology has a high specificity and that RNA-based NGS is preferable to DNA-based NGS for fusion detection. (p. NSCL-H, 5 of 7)

The NCCN guideline for Cervical Cancer (1.~~2023~~2024) suggests performing *RET* gene fusion testing for patients with locally advanced or metastatic cervical cancer of the following pathologies: squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. (p. CERV-A, 1 of 3)

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

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

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

Tumor Specific *ROS1* Gene Rearrangement

National Comprehensive Cancer Network (NCCN)

NCCN Non-Small Cell Lung Cancer guidelines (~~3~~5.2023) recommend *ROS1* rearrangement testing in patients with advanced or metastatic disease of the following lung cancer pathologies: Adenocarcinoma, Large Cell, Squamous Cell, and NSCLC not otherwise specified (NOS). (p. NSCL-18)

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NCCN guidelines for Ampullary Adenocarcinoma (1.2024) recommend tumor molecular profiling for patients with locally advanced or metastatic disease. Potentially actionable somatic findings include fusions involving the *ROS1* gene. (p. AMP-3)

NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) recommend tumor molecular profiling for patients with resectable, borderline resectable, or locally advanced or metastatic disease. Potentially actionable somatic findings include fusions involving the *ROS1* gene. (p. PANC-1A, PANC-F, 1 of 12).

NCCN guidelines for Pediatric Central Nervous System Cancers (2.2023) state that broad molecular testing is required for comprehensive classification of pediatric diffuse high-grade gliomas and should include detection of fusions involving *ROS1*. (p. PEDCNS-B, 2 of 4).

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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 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.	12/23	2/27/24
Semi-annual review. In Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests, minor expansion of criteria to be consistent with guidelines (added several tumor types for coverage). Tumor Specific BCR/ABL Gene Rearrangement (Qualitative FISH and PCR) Tests, moved criteria and combined with BCR/ABL1 criteria in the Solid Tumor and Hematological Malignancies policy to align with the clinical use of these tests. In Tumor Specific *ERBB2 (HER2)* Deletion/Duplication (FISH and CISH), minor expansion of criteria to be consistent with guidelines (added several tumor types for coverage). In *NTRK* Fusion Analysis Panel, Minor expansion of criteria to be consistent with guidelines (added several tumor types for coverage). In Tumor Specific FOLR1 Protein Analysis, Clarified ovarian cancer pathology. In Tumor Specific *RET* Gene Rearrangement Tests (FISH0), minor expansion of criteria to be consistent with guidelines (added several tumor types). In Tumor Specific *ROS1* Gene Rearrangement, minor expansion of criteria to be consistent with guidelines (added several tumor types for coverage). Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	06/24	

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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.

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