

ONCOLOGY: CYTOGENETIC TESTING

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

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.

Coverage 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	UroVysion FISH (ARUP Laboratories)	88120, 88121	C67, D09.0, D49.4, R31.9,	14, 16

Tests			Z85.51	
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
	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, 3, 5, 6, 11, 12, 18, 21, 22
Multiple Myeloma FISH Panel Analysis	Oncology FISH Analysis - Multiple Myeloma FISH Panel (Baylor Genetics, LLC)	88271, 88237, 88275, 88291	C90	13
	Multiple Myeloma (MM) FISH Profile (Labcorp)			
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, 8, 9, 11, 12, 15, 17, 18, 19, 20, 21, 22, 24, 25, 26
Tumor Specific PD-L1 Protein Analysis	PD-L1, IHC with Interpretation (Quest Diagnostics)	88341, 88342, 88360, 88361	C11, C15, C16, C34, C50, C51,	1, 3, 5, 6, 11,

			C53, C67	12, 14, 15
Tumor Specific FOLR1 Protein Analysis	FOLR1 Immunohistochemistry Analysis (Labcorp)	88360	C56	21
Tumor Specific PML/RARA Gene Rearrangement (Qualitative FISH and PCR)	FISH, AML M3, PML/RARA, Translocation 15, 17 (Quest Diagnostics)	81315, 81316, 88271, 88274, 88275, 88291	C91-C95	7
	PML/RARA t(15;17) (NeoGenomics Laboratories)			
Tumor Specific RET Gene Rearrangement (FISH)	RET FISH (NeoGenomics Laboratories)	88374, 88377, 88271, 88275, 88291	C34, C53, C73	1, 2, 3, 4, 11, 22
	Oncology FISH Analysis - RET Rearrangement (Baylor Genetics)			
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 coverage criteria for oncology-related cytogenetic testing. Please refer to:

- **Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies** for criteria related to DNA testing of a solid tumor or a blood cancer.
- **Genetic Testing: Hereditary Cancer Susceptibility Syndromes** for coverage criteria related to genetic testing for hereditary cancer predisposition syndromes.
- **Oncology: Cancer Screening** for coverage criteria related to the use of non-invasive fecal, urine, or blood tests for screening for cancer.
- **Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)** for criteria related to circulating tumor DNA (ctDNA) or circulating tumor

cell testing performed on peripheral blood for cancer diagnosis, management, and surveillance.

- **Oncology: Algorithmic Testing** for coverage criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- **Genetic Testing: Exome and Genome Sequencing for the Diagnosis of Genetic Disorders** for coverage criteria related to whole genome and whole exome sequencing in rare genetic syndromes.
- **Genetic Testing: General Approach to Genetic and Molecular Testing** for coverage criteria related to cytogenetic testing in oncology that is not specifically discussed in this or another non-general policy.

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COVERAGE 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 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**
8. Locally advanced/metastatic ampullary adenocarcinoma, **OR**
9. Langerhans cell histiocytosis, **OR**
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 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) in solid tumors is considered **medically necessary** when:
 - A. The member has any of the following:
 1. Recurrent or newly diagnosed stage I-IV invasive breast cancer, **OR**
 2. Suspected or documented metastatic gastric cancer, **OR**
 3. Suspected or proven metastatic colorectal cancer or appendiceal adenocarcinoma, **OR**
 4. Suspected or proven metastatic esophageal and/or esophagogastric junction adenocarcinoma, **OR**
 5. Recurrent, unresectable, or metastatic salivary gland tumors, **OR**
 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 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 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**
 - 10. Metastatic uterine sarcoma, **OR**
 - 11. Recurrent unresectable or stage IV invasive breast cancer, **OR**
 - 12. Unresectable locally [advanced](#), recurrent, or metastatic gastric cancer, **OR**

13. Unresectable locally [advanced](#), recurrent, or metastatic esophageal cancer, **OR**
14. Anaplastic thyroid carcinoma or locally recurrent, [advanced](#), and/or metastatic papillary, follicular, or oncocytic carcinoma (formerly called Hurthle cell carcinoma), **OR**
15. Acute lymphoblastic leukemia (ALL), **OR**
16. Advanced or metastatic soft tissue sarcoma, **OR**
17. Unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm, **OR**
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 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 has 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 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 has a diagnosis of:
 1. Recurrent or persistent locoregional or metastatic medullary thyroid cancer, **AND**
 - a) Germline testing for *RET* mutations is negative or has not been done, **OR**
 2. Anaplastic thyroid carcinoma, **OR**
 3. Locally recurrent, [advanced](#) and/or metastatic papillary thyroid carcinoma, **OR**
 4. Locally recurrent, advanced and/or metastatic follicular thyroid carcinoma, **OR**
 5. Locally recurrent, advanced and/or metastatic oncocytic carcinoma (formerly called Hurthle cell carcinoma), **OR**
 6. [Advanced](#) or metastatic adenocarcinoma of the lung, **OR**
 7. [Advanced](#) or metastatic large cell cancer of the lung, **OR**

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

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Tumor Specific *ROS1* Gene Rearrangement

- I. Tumor specific *ROS1* gene rearrangement analysis via fluorescent in situ hybridization (FISH) (88271, 88274) in solid tumors is considered **medically necessary** when:
 - A. The member 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. 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:** 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 (4.2023) recommend that individuals with anaplastic thyroid cancer should undergo molecular testing including *BRAF*, *NTRK*, *ALK*, *RET*, MSI, dMMR, and tumor mutational burden if not previously done (p. ANAP-1). *ALK* testing is also recommended for locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma (p. PAP-10) and locally recurrent, advanced, and/or metastatic follicular thyroid carcinoma (p. FOLL-9).

NCCN Non-Small Cell Lung Cancer guidelines (2.2024) recommend *ALK* rearrangement testing in patients with Stage IB-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)

NCCN guidelines for Ampullary Adenocarcinoma (1.2024) recommend somatic molecular profiling for patients with locally advanced/metastatic disease who are

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

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

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

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

Bladder Cancer Diagnostic and Recurrence FISH Tests

National Comprehensive Cancer Network (NCCN)

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

American Urological Association and Society of Urologic Oncology

The American Urological Association and Society of Urologic Oncology (2016; amended 2020) addressed the diagnosis and treatment of non-muscle-invasive bladder

cancer, based on a systematic review and includes the following statements on the use of urine markers after the diagnosis of bladder cancer:

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

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

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

National Comprehensive Cancer Network (NCCN)

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

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

National Comprehensive Cancer Network (NCCN)

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

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

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

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

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

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

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

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

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

Multiple Myeloma FISH Panel Analysis

National Comprehensive Cancer Network (NCCN)

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

NTRK Fusion Analysis Panel

National Comprehensive Cancer Network (NCCN)

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

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

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

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

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

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

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

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

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

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

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

The NCCN Soft Tissue Sarcoma guidelines (3.2023) state that larotrectinib and entrectinib have demonstrated efficacy in patients with *NTRK* positive tumors and are recommended as first line treatment options for patients with advanced or metastatic *NTRK* positive sarcomas. (p. MS-29)

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

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

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

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

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

The NCCN Pediatric Central Nervous System Cancers guidelines (2.2023) state that broad molecular testing is required for comprehensive classification of pediatric diffuse

high-grade gliomas, including NGS with fusion detection for *ROS1*, *MET*, *NTRK1/2/3*, *ALK*, *FGFR1/2/3*. (p. PEDCNS-B, 2 of 4)

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

Tumor Specific PD-L1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

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

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

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

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

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

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

NCCN Non-Small Cell Lung Cancer guidelines (2.2024) recommend PD-L1 testing in patients with stage IB-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 (1.2024) recommends PD-L1 testing for individuals with recurrent or stage IV triple negative breast cancer. (p. BINV-R 1 of 3)

Tumor Specific FOLR1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

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

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

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

National Comprehensive Cancer Network (NCCN)

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

Tumor Specific *RET* Gene Rearrangement (FISH)

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Thyroid Carcinoma (4.2023) recommend molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS. Germline and somatic *RET* testing is recommended in all individuals with newly diagnosed medullary thyroid carcinoma. For patients with recurrent or persistent

MTC, somatic *RET* testing is recommended if germline wild type or germline unknown (p. MEDU-6). Additionally they comment that molecular testing has shown to be beneficial when making targeted therapy decisions. (p. THYR-B) The guideline also comments that individuals with anaplastic thyroid cancer and/or metastatic disease should undergo molecular testing including *BRAF*, *NTRK*, *ALK*, *RET* and tumor mutational burden if not previously done. (p. ANAP-3)

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

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

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

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

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

Tumor Specific *ROS1* Gene Rearrangement

National Comprehensive Cancer Network (NCCN)

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

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

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

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

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