Revision log
Coding Implications

CONCERT GENETIC ONCOLOGY: CYTOGENETIC TESTING

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 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. 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, associated laboratories, CPT codes, and ICD 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 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* FISH, Non-Small cell Lung Cancer (Labcorp)	88271, 88274	C34, C73	1, 4, 21, 22, 23, 26
Bladder Cancer Diagnostic and Recurrence FISH Tests	UroVysion Bladder Kit (Quest Diagnostics)	88120, 88121	C67, R31.9, Z85, Z85.5	30, 31
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis	FISH for Chronic Lymphocytic Leukemia (Cleveland Clinic Laboratories) FISH, B-Cell Chronic Lymphocytic Leukemia Panel (Quest Diagnostics)	88271, 88274, 88275, 88291	C91, C94, C95, Z85.6	10
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, 14, 17, 20, 21, 25, 27
Multiple Myeloma FISH Panel Analysis	Oncology FISH Analysis - Multiple Myeloma FISH Panel (Baylor Genetics, LLC) Multiple Myeloma (MM) Profile, FISH (Labcorp)	88237, 88271, 88275, 88291	C90	13
NTRK Fusion Analysis Panel	*NTRK* NGS Fusion Panel (NeoGenomics Laboratories)	81191, 81192, 81193, 81194	C15, C16, C18, C34, C49.9, C50,	1, 2, 3, 4, 5, 6, 8, 9,

			C51, C53, C54, C73, C80.1, C91	11, 12, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 27, 32, 33
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, 11, 12, 14, 15, 27, 28, 29
Tumor Specific FOLR1 Protein Analysis	FOLR1 Immunohistochemistry Analysis (Labcorp)	88360	C56	20
Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR)	FISH, APL, *PML/RARA*, Translocation 15, 17 (Quest Diagnostics) PML/RARA t(15;17) (NeoGenomics Laboratories)	81315, 81316, 88271, 88274, 88275, 88291	C91-C95	7
Tumor Specific *RET* Gene Rearrangement Tests (FISH)	*RET* FISH (NeoGenomics Laboratories) Oncology FISH Analysis - *RET* Rearrangement (Baylor Genetics)	88271, 88275, 88291, 88374, 88377	C34, C53, C73	1, 2, 3, 4, 5, 6, 11, 21, 27
Tumor Specific *ROS1* Gene Rearrangement	FISH ROS1 Rearrangement (Johns Hopkins Medical Institutions-Pathology Laboratory)	88271, 88274	C34	1, 21, 22, 23

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.

back to top

CRITERIA

It is the policy of health plans affiliated with Centene Corporation® 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**
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.

back to top

Bladder Cancer Diagnostic and Recurrence FISH Tests

I. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for diagnosing, and monitoring bladder cancer are considered **medically necessary** when:

A. The member/enrollee has hematuria, **AND**

1. Diagnostic studies have failed to identify the etiology of the hematuria, **AND**
2. A bladder cancer diagnostic and recurrence FISH test has not been ordered more than 1 time in the past 12 months, **OR**

B. The member/enrollee has been treated for bladder cancer, **AND**

1. The bladder cancer diagnostic and recurrence FISH tests are ordered with the following frequency:

a) No more than 4 bladder tumor marker studies per year for years 1-2 after diagnosis

b) No more than 3 bladder tumor marker studies per year during year 3 after diagnosis

c) No more than 2 bladder tumor marker studies during year 4 after diagnosis

d) No more than 1 bladder tumor marker studies annually for up to 15 years after diagnosis.

II. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for screening of member/enrollee with hematuria are considered **investigational**.

III. Bladder cancer diagnostic and recurrence FISH tests (88120, 88121) for diagnosing, and monitoring bladder cancer are considered **investigational** for all other indications.

back to top

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).

back to top

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/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, **OR**

3. Suspected or proven metastatic colorectal cancer or appendiceal adenocarcinoma, **OR**
4. Inoperable locally advanced, recurrent or 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. Endometrial carcinosarcoma, **OR**
9. p53 abnormal endometrial carcinoma, **OR**
10. Resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma, **OR**
11. Recurrent ovarian/fallopian tube/primary peritoneal cancer, **OR**
12. Recurrent or metastatic vaginal cancer, **OR**
13. Stage IIIB or higher muscle invasive bladder cancer, **OR**
14. Metastatic small bowel adenocarcinoma.

back to top

Multiple Myeloma FISH Panel Analysis

I. Multiple myeloma FISH panel analysis (88237, 88271, 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.

back to top

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, progressive, or metastatic solid tumor, **OR**
2. Cancer for which surgical resection is not possible, **OR**
3. Unknown primary cancers, **OR**

B. The member/enrollee has a diagnosis of any of the following cancers at any stage:

1. Cervical sarcoma, **OR**
2. Anaplastic thyroid carcinoma, **OR**
3. Acute lymphoblastic leukemia (ALL), **OR**
4. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma.

back to top

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

NOTE: PD-L1 protein expression analysis via IHC is often performed as an adjunct component of comprehensive molecular profiling panels for solid tumors

back to top

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 recurrent, platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer, **AND**

B. Elahere (mirvetuximab soravtansine) is being considered for treatment.

back to top

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).

back to top

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. Recurrent or persistent locoregional or metastatic medullary thyroid cancer, **AND**

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

2. Anaplastic thyroid carcinoma, **OR**

3. Locally recurrent, advanced and/or metastatic papillary thyroid carcinoma, **OR**

4. Locally recurrent, advanced and/or metastatic follicular thyroid carcinoma, **OR**

5. Locally recurrent, advanced and/or metastatic oncocytic carcinoma (formerly called Hurthle cell carcinoma), **OR**

6. Advanced or metastatic adenocarcinoma of the lung, **OR**

7. Advanced or metastatic large cell cancer of the lung, **OR**

8. Advanced or metastatic non-small cell cancer of the lung, not otherwise specified, **OR**

9. Locally advanced or metastatic squamous cell carcinoma of the cervix, **OR**

10. Locally advanced or metastatic adenocarcinoma of the cervix, **OR**

11. Locally advanced or metastatic adenosquamous carcinoma of the cervix, **OR**
12. Recurrent unresectable or stage IV breast cancer, **OR**
13. Suspected or confirmed metastatic colon cancer, **OR**
14. Resectable, borderline resectable, locally advanced or metastatic pancreatic adenocarcinoma, **OR**
15. Locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer, **OR**
16. Locally advanced, recurrent or metastatic gastric cancer, **OR**
17. Recurrent or metastatic vaginal cancer.

back to top

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/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), **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.

back to top

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.

back to top

BACKGROUND AND RATIONALE

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

National Comprehensive Cancer Network (NCCN)

The NCCN Thyroid Carcinoma guidelines (3.2024) recommend that individuals with anaplastic thyroid cancer should undergo molecular testing including *BRAF, NTRK, ALK, RET*, MSI, dMMR, and tumor mutational burden if not previously done (p. ANAP-1). *ALK* testing is also recommended for locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma (p. PAP-10) and locally recurrent, advanced, and/or metastatic follicular thyroid carcinoma. (p. FOLL-9)

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

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

NCCN guidelines for Histiocytic Neoplasms (2.2024) recommends molecular testing of a tissue biopsy during the diagnostic workup for Langerhans cell histiocytosis and Erdheim-Chester disease, and suggests RNA based molecular panel including fusion testing for *ALK*; however if *ALK* rearrangement is suspected clinically, or if fusion panel testing is not available, ALK immunohistochemistry and FISH studies may be performed. (p. LCH-2, ECD-2)

NCCN guidelines for Pancreatic Adenocarcinoma (3.2024) recommend somatic molecular profiling for patients with locally advanced/metastatic disease as well as those with resectable or borderline resectable disease if systemic therapy is being considered. Potentially actionable somatic findings include fusions involving the ALK gene. (p. PANC-1A)

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

Bladder Cancer Diagnostic and Recurrence FISH Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled "Lab: Bladder/Urothelial Tumor Markers" includes the following utilization guidelines for bladder marker testing.

Regarding the UroVysion Bladder Cancer Kit: "It is used to detect chromosomal abnormalities in voided urine to assist not only in bladder cancer surveillance but also in the initial identification of bladder cancer."

"*Follow-up after initial diagnosis/most recent occurrence and treatment*

- Maximum of 4 bladder tumor marker studies per year for years 1-2
- Maximum of 3 bladder tumor marker studies per year for year 3
- Maximum of 2 bladder tumor marker studies for year 4 and
- Maximum of 1 bladder tumor marker studies follow-up annually for up to 15 years."

"For high risk patients with persistent hematuria and a negative FISH assay following a comprehensive diagnostic (no tumor identified) workup, ONE repeat FISH testing in conjunction with cystoscopy is considered reasonable and necessary within 1 year of the original attempted diagnosis."

The CMS LCD Reference Article "Billing and Coding: Lab: Bladder/Urothelial Tumor Markers" states the following: "This A/B MAC will only cover bladder tumor marker fluorescence in situ hybridization (FISH) testing services when performed using validated assays. To date, UroVysion Bladder Cancer Kit is the only Federal Drug Administration (FDA) approved assay that is designed to detect aneuploidy for chromosomes 3, 7, 17 and loss of the 9p21 locus via FISH.

Bladder cancer tumor markers performed by any technology, immunoassay, molecular or FISH testing, are not covered for screening of all patients with hematuria."

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

National Comprehensive Cancer Network (NCCN)

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

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

National Comprehensive Cancer Network (NCCN)

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

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

NCCN Colon Cancer guidelines (4.2024) recommend HER2/*ERBB2* testing during the workup for suspected or proven metastatic colorectal cancer. (p. COL-2) These guidelines also recommend HER2 analysis for metastatic appendiceal adenocarcinoma. (p. COL-I 2 of 3)

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

NCCN Breast Cancer guidelines (4.2024) recommend HER2/*ERBB2* testing be performed on all patients with newly diagnosed primary or metastatic breast cancer. (p. BINV-A 1 of 2)

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

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

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

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

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

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

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

Multiple Myeloma FISH Panel Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Multiple Myeloma guidelines (4.2024) recommend FISH testing during the initial workup of multiple myeloma for prognostic purposes. The recommended FISH testing includes: del(13), del (17p13), t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/1q21 amplification, 1p deletion. (p. MYEL-1)

***NTRK* Fusion Analysis Panel**

National Comprehensive Cancer Network (NCCN)

The NCCN Thyroid Carcinoma guidelines (3.2024) recommend that individuals with anaplastic thyroid cancer or locally recurrent, advanced, and/or metastatic papillary, follicular, and oncocytic carcinoma (formerly called Hurthle cell carcinoma) undergo molecular testing including NTRK as part of disease workup. (p. ANAP-1, p. PAP-10, p. FOLL-9, p. ONC-9)

The NCCN Colon Cancer Guidelines (4.2024) recommend broad molecular profiling to identify rare and actionable mutations and fusions, including NTRK, for patients with suspected or proven metastatic adenocarcinoma. (p. COL-2) For individuals who are *NTRK* gene fusion-

positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib. (p. COL-D 2 of 11)

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

The NCCN Occult Primary guidelines (1.2025) states that patients with metastatic or unresectable *NTRK* gene fusion positive adenocarcinomas without a known acquired resistance mutation, who have no satisfactory treatment options or who have progressed on treatment can be treated with entrectinib and/or larotrectinib or repotrectinib. (p. OCC-B, 2 of 11)

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

The NCCN Vulvar Cancer guidelines (4.2024) recommends consideration of *NTRK* fusion analysis for recurrent, progressive, or metastatic squamous cell carcinoma of the vulva. (p. VULVA-A 2 of 4)

The NCCN Uterine Neoplasms guidelines (2.2024) recommends consideration of *NTRK* fusion analysis for recurrent or metastatic endometrial carcinoma (p. ENDO-A 2 of 4) or metastatic uterine sarcoma. (p. UTSARC-A 1 of 8)

The NCCN Breast Cancer guidelines (4.2024) recommend NTRK fusion testing for recurrent unresectable or stage IV disease if eligible for larotrectinib, entrectinib or repotrectinib treatment (no known resistance mutation and no satisfactory alternatives or have progressed on treatment). (p. BINV-Q 6 of 14)

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

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

The NCCN Acute Lymphoblastic Leukemia guidelines (2.2024) and Pediatric Acute Lymphoblastic Leukemia guidelines (6.2024) recommend *NTRK* fusion analysis for acute

lymphoblastic leukemia (ALL) for the purposes of risk stratification. (p. ALL-3; p. PEDALL-A 1 of 2)

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

The NCCN Neuroendocrine and Adrenal Tumors guidelines (2.2024) recommends consideration of *NTRK* fusion testing for patients with unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm. (p. PDNEC-1) For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib. (p. NE-H 5 of 9

The NCCN Head and Neck Cancers guidelines (4.2024) recommend use of NGS profiling and other appropriate biomarker testing to evaluate *NTRK* prior to treatment for metastatic salivary gland tumors. (p. SALI-4)

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

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

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

The NCCN Pediatric Central Nervous System Cancers guidelines (1.2024) state that broad molecular testing is required for comprehensive classification of pediatric diffuse high-grade gliomas, including NGS with fusion detection for *ROS1*, *MET*, *NTRK1/2/3*, *ALK*, *FGFR1/2/3*. (p. PGLIO-B, 2 of 4)

The NCCN guidelines for Pancreatic Adenocarcinoma (3.2024) recommend testing for potentially actionable somatic findings including *NTRK* fusions for patients with locally advanced/metastatic disease. (p. PANC-1A) In addition, patients with resectable or borderline resectable disease who are considering systemic therapy are recommended to consider testing for somatic findings including NTRK fusions. (p. PANC-F, 1 of 12) For individuals who are *NTRK*

gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib. (p. PANC-F 3 of 12)

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

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

Food and Drug Administration

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

- "adult patients with locally advanced or metastatic ROS1-positive nonsmall cell lung cancer (NSCLC). (1.1)
- adult and pediatric patients 12 years of age and older with solid tumors that:
    - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and
    - are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.

have progressed following treatment or have no satisfactory alternative therapy.

Tumor Specific PD-L1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

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

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

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

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

The NCCN Esophageal and Esophagogastric Junction Cancers guidelines (4.2024) recommends PD-L1 testing for individuals during the workup phase for documented or suspected metastatic esophageal and esophagogastric junction cancers. (p. ESOPH-1)

The NCCN Cervical Cancer guidelines (3.2024) recommends PD-L1 testing for individuals with recurrent, progressive, or metastatic cervical cancer of the following pathologies: squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. (p. CERV-A 1 of 7)

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

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

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

Food and Drug Administration (FDA)

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

Tumor Specific FOLR1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (3.2024) indicate that the preferred treatment regimen for platinum resistant recurrent disease includes mirvetuximab soravtansine if the tumor expresses folate receptor alpha (i.e., FOLR1). Therefore, tumor molecular analysis for this cancer type is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit, including folate receptor alpha (FOLR1). (p. OV-C, 9 and 10 of 12)

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

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

National Comprehensive Cancer Network (NCCN)

NCCN Acute Myeloid Leukemia guidelines (3.2024) state that many different types of gene mutations are associated with specific prognoses, helping to guide medical management decisions, and/or may indicate that specific therapeutic agents are useful. Therefore, all patients with AML should be tested for these mutations. (p. EVAL-1). The discussion section of this guideline states that *PML-RAR* alpha is included in this group of genetic markers that should be tested in all patients. (p. MS-4)

Tumor Specific *RET* Gene Rearrangement Tests (FISH)

National Comprehensive Cancer Network (NCCN)

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

The NCCN guideline on Non-Small Cell Lung Cancer (7.2024) recommends analysis for *RET* gene rearrangements in patients with advanced or metastatic adenocarcinoma of the lung, large cell carcinoma of the lung, or NSCLC not otherwise specified and recommends consideration of RET gene testing for patients with advanced or metastatic squamous cell carcinoma of the lung (p. NSCL-19), noting that NGS-based methodology has a high specificity and that RNA-based NGS is preferable to DNA-based NGS for fusion detection. (p. NSCL-H, 5 of 8)

The NCCN guideline for Cervical Cancer (3.2024) recommends consideration of *RET* gene fusion testing for patients with locally advanced or metastatic cervical cancer of the following pathologies: squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. (p. CERV-A, 1 of 7)

NCCN guidelines for Breast Cancer (4.2024) list *RET* fusion as a biomarker with an FDA approved therapy for any subtype of recurrent unresectable or stage IV disease. Either tumor tissue or blood can be used for detection. (p. BINV-Q, 6 of 14)

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

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

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

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

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

Tumor Specific *ROS1* Gene Rearrangement

National Comprehensive Cancer Network (NCCN)

NCCN Non-Small Cell Lung Cancer guidelines (7.2024) recommend *ROS1* rearrangement testing in patients with advanced or metastatic disease of the following lung cancer pathologies: Adenocarcinoma, Large Cell, and NSCLC not otherwise specified (NOS) and recommends consideration of this testing for patients with squamous cell carcinoma of the lung. (p. NSCL-19)

NCCN guidelines for Ampullary Adenocarcinoma (2.2024) recommend consideration of tumor molecular profiling, including for ROS1 fusions, for patients with locally advanced or metastatic disease who are considering systemic therapy. (p. AMP-3)

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

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

back to top

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. 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.	10/23	10/23
Semi-annual review. Updated title to reflect V2.2024 version. 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	04/24	04/24

Reviews, Revisions, and Approvals	Revision Date	Approval Date
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.		
Semi-annual review. Updated title to reflect V1.205 verison. NTRK Fusion Analysis Panel: Added all metastatic, progressive, advanced, inoperable, or unknown solid tumors to the criteria for testing and reworded the criteria to reflect a change in NCCN guidelines; Added cancer type for coverage (recurrent or metastatic vaginal cancer) based on NCCN guidelines; Added discussion and new NCCN and FDA references in the Background & References to support criteria changes; Updated NCCN version numbers in Background and Rationale and References. Tumor Specific ERBB2 (HER2) Deletion/Duplication (FISH and CISH): Added cancer types for coverage (p53 abnormal endometrial carcinoma, Recurrent or metastatic vaginal cancer, Stage IIIB or higher muscle invasive bladder cancer, Metastatic small bowel adenocarcinoma) based on NCCN guidelines; Updated NCCN version numbers in Background and Rationale and References. Tumor Specific PD-L1 Protein Analysis: Added cancer type for coverage (recurrent or metastatic vaginal cancer) based on NCCN guidelines; Updated NCCN version numbers in Background and Rationale and References, added additional references to support coverage. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis: Updated NCCN version in Background and Rationale and references. Multiple Myeloma FISH Panel Analysis: Updated NCCN version in Background and Rationale and references. Tumor Specific PML/RARA Gene Rearrangement (Qualitative FISH and PCR): Updated NCCN version in Background and Rationale and References. Tumor Specific ALK Gene Rearrangement (Qualitative FISH and PCR) Tests: Updated NCCN version in Background and Rationale and References. Bladder Cancer Diagnostic and Recurrence FISH Tests: Coverage status changed from non-covered to covered based on LCD guidelines; Updated reference numbers in Policy Reference Table; Streamlined portions of Background and Rationale section for brevity; Updated References. Tumor Specific ROS1 Gene Rearrangement: Updated NCCN version in Background and Rationale and References. Tumor Specific FOLR1 Protein Analysis: Updated NCCN version in Background and Rationale and References. Tumor Specific RET Gene Rearrangement Tests (FISH): Added cancer types for coverage (Locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer, Locally advanced, recurrent or metastatic gastric cancer, Recurrent or metastatic vaginal cancer) based on NCCN guidelines; Updated NCCN version in Background and Rationale and References.	11/24	11/24

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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. The Health Plan 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. “Health Plan” means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

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 Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. 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. The Health Plan 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 member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/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 the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.

back to top