Effective for dates of service on and after **November 15, 2026**, the following updates will apply to Carelon Medical Benefits Management, Inc. Clinical Appropriateness Guidelines. As part of the Carelon guideline annual review process, these updates are focused on advancing efforts to drive clinically appropriate, safe, and affordable health care services.

Genetic Testing

Multiple guidelines (Genetic Liquid Biopsy and Somatic Tumor Testing)

- General Criteria
    - Added requirement that all components of a test must demonstrate clinical utility

Genetic Liquid Biopsy in the Management of Cancer and Cancer Surveillance

- General Information
    - Added definition of circulating tumor-tissue-modified viral HPV DNA (ctHPV DNA)
    - Added clarification for monitoring and surveillance setting – MRD
- General Criteria for Genetic Liquid Biopsy Testing
    - Added criterion that RNA fusion, expression, and whole transcriptome analysis using ctRNA is not medically necessary
    - Add exception for reflex tissue biopsy after liquid biopsy if an actionable variant result is not detected or uninformative
- Breast carcinoma
    - Expanded the stages of breast cancer for which molecular profile testing is indicated from metastatic and added recurrent and locally advanced, i.e., AJCC stages stage IIB IIIA, IIIB, or IIIC disease, or inoperable IIB disease)
    - Added the new drug imlunestrant to the list of therapies for which ESR1 mutation testing is considered medically necessary
- Prostate carcinoma
    - Added the drug niraparib to the list of therapies for which testing is considered medically necessary
- ctDNA for Molecular Residual Disease (MRD) or Therapy Response
    - Clarified use of ctDNA to assess therapy response, added common indications where MRD testing is not medically necessary, and added test examples
- ctHPV DNA Testing for Recurrence, Surveillance, Post-Treatment Molecular Residual Disease or Therapy Response
    - New criterion that use of ctHPV DNA testing in oropharyngeal carcinoma is not medically necessary
- Blood-based cfDNA Testing for Colorectal Cancer Screening
    - Added criteria for blood-based cfDNA tests for colorectal cancer screening in average-risk individuals age 45 years or older. Added examples for medically necessary FDA-approved tests Shield™ and SimpleScreen™ CRC when criteria are met
    - Added not medically criteria given importance of strict criteria for use of these tests
    - Removed Shield, as this test is now FDA approved and considered medically necessary per above criteria

- Individuals without Malignancy for whom Liquid Biopsy is Used for Screening
    - Added test examples including CancerGuard®

Somatic Tumor Testing

Solid Tumors

- General Requirements
    - Added clarifying statement to ensure testing is performed in CLIA certified lab
- General Criteria
    - Added general requirement that all components of a test must demonstrate clinical utility
    - Allow targeted RNA-based fusion analysis using NGS if noted in the cancer-specific criteria (applies to Tissue-agnostic testing, Biliary Tract Cancer, Bladder Cancer, Brain Cancer, Non-small Cell Lung Cancer, Pancreatic Adenocarcinoma, Sarcoma, Thyroid Cancer, and Unknown Primary Site Cancer)
    - Added exception for reflex tissue biopsy after liquid biopsy if an actionable variant result is not detected or uninformative
- Tissue-agnostic Testing for Patients with Advanced Solid Tumors
    - Allow targeted RNA-based fusion testing
    - Allow HER2 testing
    - Removed criterion for FGFR1/2/3 fusions or pathogenic/likely pathogenic (P/LP) variants
- Biliary Tract Cancer (including Cholangiocarcinoma and Gallbladder Cancer)
    - Allow targeted RNA-based fusion testing
    - Comprehensive molecular testing is required to include list of genes that should be tested
- Bladder Cancer (Urothelial Carcinoma, including the Upper Tract)
    - Allow targeted RNA-based fusion testing
    - Included all patients with unresectable or metastatic bladder cancer at the time of initial diagnosis (removed “potential”)
- Brain Cancer (Malignant Glioma)
    - Allow targeted RNA-based fusion testing
    - Included P/LP variants of H3 K27M in response to FDA approval of dordaviprone (Modeyso™) in adults and children with diffuse midline gliomas
    - Included BRAF fusions/rearrangements in response to FDA approval of tovorafenib (Ojemda™) for individuals with pediatric low-grade gliomas
    - Add criteria for use of MGMT promoter methylation testing
- Breast Cancer, localized invasive; early adjuvant setting (split criteria by lymph node status)
    - Lymph node negative, lymph node omitted, or lymph node micro-metastasis
        - Premenopausal or age ≤ 50 with negative lymph node, omitted, or micrometastasis limited to Oncotype DX
            - Postmenopausal or age > 50 with negative lymph node, omitted, or micrometastasis includes all tests

        - Allow GEP testing in the premenopausal or age < 50 population if lymph node sampling is omitted
    - Axillary lymph node status (1-3 positive)
        - Included EndoPredict in this clinical setting
        - Allow testing in axillary lymph node status positive setting, age > 50
        - Added clinical nodal status to pathologic nodal status
    - Testing on breast cancer recurrence is not medically necessary
- Breast Cancer, localized; extended adjuvant setting
    - Added clarification on timeframe for performing testing in the extended adjuvant setting
    - Testing on breast cancer recurrence is not indicated
- Breast Cancer, metastatic and/or locally advanced
    - Expanded treatment list to include imlunestrant for which molecular testing is indicated
- Colorectal Cancer, localized
    - Added PIK3CA testing as predictive biomarker
- Colorectal Cancer, metastatic
    - Added MSI testing, if not previously performed
    - Added KRAS variant p.G12C to extended RAS testing associated with specific therapy
- Endometrial Carcinoma
    - Added clarification to allow for multigene panel testing at any stage to include any of the listed genes
- Melanoma
    - Added clarification on the use of GEP testing in indeterminate cutaneous lesions in not medically necessary and provided test example
    - Provided test examples that are not medically necessary in prognostication
- Non-small Cell Lung Cancer, localized (stage IB-IIIA)
    - Added clarification that testing for targeted therapy in the perioperative/adjuvant setting
- Non-small Cell Lung Cancer, advanced (stage IIIB, IIIC, or IV metastatic)
    - Allow RNA-based fusion testing
    - Expand the basis for rebiopsy from progression on targeted therapies (i.e., therapy based on ALK/ROS1/RET/MET/BRAF/HER2/KRAS G12C/NTRK)
- Ovarian (Epithelial) Cancer
    - Include fallopian tube and primary peritoneal cancers
    - Added maintenance therapy indication for homologous recombination deficiency (HRD) testing
- Pancreatic Adenocarcinoma
    - Allow targeted RNA-based fusion testing
    - Remove stage requirements for testing
- Prostate Cancer, localized
    - Added clarification on not medically necessary gene expression profiling tests with examples
- Prostate Cancer, metastatic
    - Removed requirement for “adenocarcinoma” and broaden to prostate cancer

    - Removed requirement for metastatic castrate sensitive adenocarcinoma (mCSPC) with high burden of disease to allow testing in all metastatic clinical indications
    - Added eligible PARP inhibitor therapies (niraparib, talazoparib)
    - Added "deficient" for HRD testing result for clarity
    - Included additional genes that can be considered for multigene panel testing
- Sarcoma (including soft tissue sarcoma, bone sarcoma, gastrointestinal stromal tumor, uterine sarcoma)
    - Allow targeted RNA-based fusion testing
    - Include testing for resistance mutations with a change in clinical status while on targeted therapy if other therapies may be indicated
- Thyroid Neoplasm, noninvasive follicular with papillary-like nuclear features (NIFTP)
    - Somatic testing of NIFTP is not medically necessary
- Thyroid Cancer, recurrent or persistent locoregional medullary cancer
    - Included positive criteria for testing in medullary thyroid cancer
- Thyroid Cancer, metastatic, locally advanced, recurrent, progressive, symptomatic
    - Included positive criteria for locally advanced, recurrent, progressive, symptomatic thyroid cancer
    - Removed gene number restriction
    - Added genes and tumor mutational burden (TMB) testing that can be considered in thyroid cancer
- Thyroid Cancer, anaplastic thyroid cancer
    - Added genes and TMB testing that can be considered
    - Unknown Primary Site Cancer
    - Include positive criteria for MSI in cancers of unknown origin
    - Include positive criteria for multigene panel testing in cancers of unknown origin
    - Include list of genes that should be tested
- Whole Exome (WES), Whole Genome (WGS), and Whole Transcriptome Analysis (WTA)
    - WES, WGS and WTA are considered not medically necessary

Hematologic Malignancies

- Tissue, Bone Marrow, or Blood-Agnostic Testing for Patients with Hematological Cancers
    - Added not medically necessary statement for clarity
    - Added targeted RNA fusion analysis if noted in cancer-specific criteria (applies to Acute Lymphoblastic Leukemia and pediatric B-cell Precursor Lymphoblastic Lymphoma, Acute Myelogenous Leukemia)
- Acute Lymphoblastic Leukemia and Pediatric B-cell Precursor Lymphoblastic Lymphoma
    - Allow targeted RNA fusion analysis
    - Added genes that can be included in a 50 or fewer gene multigene panel
- Acute Myelogenous Leukemia
    - Allow targeted RNA fusion analysis
    - Added clarification defining core binding factor molecular subtypes
- B-cell Lymphomas
    - Allow testing on lymph node tissue
    - Expanded testing to stratify risk or to identify actionable therapeutic targets

- Chronic Lymphocytic Leukemia
    - Multigene panel must include testing of the TP53 gene
    - Multigene panel may include testing of optional genes
- Myeloproliferative Neoplasms
    - Non-hematologic abnormalities included as criterion for molecular testing in the absence of hematologic abnormalities including unexplained splanchnic, cerebral, or arterial thrombosis
- Myelodysplastic Syndrome
    - Added clarification on when peripheral blood can be used
    - Additional genes listed that can be included in multigene panel testing
- Multiple Myeloma
    - Included criteria where NGS or molecular testing are not indicated with examples of test
    - Added NGS or molecular testing positive criteria for multiple myeloma
- Measurable Residual Disease (MRD)
    - Added clarification of MRD testing landmarks
    - Clarification on MRD testing situations that are not medically necessary
- Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma
    - Clarified that gene expression testing is not medically necessary
    - Added positive criteria for Waldenström macroglobulinemia/lymphoplasmacytic lymphoma