Broad Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)

I. Broad molecular profiling panel tests via circulating tumor DNA (ctDNA) (liquid biopsy) are considered **medically necessary** when:

A. The member has a diagnosis, progression, or recurrence of one of the following:

1. Locally advanced/metastatic pancreatic adenocarcinoma, **OR**
2. Metastatic or advanced gastric cancer, **OR**
3. Metastatic or advanced esophageal or esophagogastric junction cancer, **OR**
4. Metastatic prostate cancer, **OR**
5. Stage III or IV cutaneous melanoma, **OR**
6. Metastatic colorectal cancer, **OR**
7. Locally advanced or metastatic ampullary adenocarcinoma, **OR**
8. Persistent or recurrent cervical cancer, **OR**
9. Unresectable or metastatic biliary tract cancer, **OR**
10. Suspected or confirmed histiocytic neoplasm, **OR**
11. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine neoplasms, **OR**
12. Locoregional unresectable or metastatic large or small cell neuroendocrine neoplasms , **OR**
13. Locoregional unresectable or metastatic mixed neuroendocrine-non-neuroendocrine neoplasm, **OR**
14. Suspected metastatic malignancy of unknown primary with initial determination of histology, **OR**

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15. Recurrent ovarian, fallopian tube or primary peritoneal cancer, **AND**

16. At least one of the following:

    a) The member is medically unfit for invasive tissue sampling (biopsy), **OR**

    b) Biopsy was performed, but material was insufficient for molecular analysis, **OR**

    c) Biopsy was performed, but molecular analysis was not able to be completely assessed on tissue due to availability of testing methodologies, **OR**

    d) Biopsy is not possible due to location of the tumor, **OR**

B. The member is being evaluated at diagnosis, progression, or recurrence of one of the following:

    1. Recurrent or stage IV breast cancer, OR

    2. Suspected or proven metastatic rectal cancer, **OR**

    3. Suspected or proven metastatic colon cancer, **OR**

    4. Locally advanced or metastatic lung adenocarcinoma, **OR**

    5. Locally advanced or metastatic large cell lung carcinoma, **OR**

    6. Locally advanced or metastatic squamous cell lung carcinoma, **OR**

    7. Locally advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**

C. The member has a diagnosis of metastatic prostate cancer, **AND**

    1. The member is undergoing initial workup, **OR**

    2. There is biochemical or radiologic evidence of recurrence or progression as demonstrated by either of the following:

        a) Prostate specific antigen (PSA) is not undetectable, **OR**

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b) There is radiographic progression.

II. Broad molecular profiling panel tests via circulating tumor DNA (ctDNA) performed simultaneously with solid tumor tissue testing is considered **medically necessary** when the member has one of the following diagnoses:

A. Lung adenocarcinoma, **OR**

B. Large cell lung carcinoma, **OR**

C. Squamous cell lung carcinoma, **OR**

1. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

III. Broad molecular profiling panel tests via circulating tumor DNA (ctDNA) are considered **investigational** for all other indications, including being performed simultaneously with solid tumor tissue testing for tumor types other than those described above.

RATIONALE AND REFERENCES

Broad Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)

National Comprehensive Cancer Network (NCCN): Prostate Cancer (2.2025)

This guideline recommends evaluating prostate tumors for mutations in homologous recombination DNA repair genes (such as *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12*) in individuals with metastatic prostate cancer. In addition, MSI evaluation is recommended for metastatic prostate cancer. Plasma circulating tumor (ctDNA) assay is an option if biopsy is not feasible, but should be collected when there is radiographic or biochemical progression (ie elevated PSA) to reduce the risk of false negatives. In patients with undetectable PSA levels, the NCCN recommends against ctDNA collection (PROS-C, 2 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

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National Comprehensive Cancer Network (NCCN): Gastric Cancer (2.2025)

This guideline recommends consideration of a liquid biopsy based comprehensive genomic profiling assay in patients who have metastatic or advanced gastric cancer who may be unable to safely undergo a traditional biopsy (p. GAST-B 6 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline recommends tumor molecular profiling for patients with locally advanced, metastatic disease, recurrence after resection, or disease progression if anti-cancer treatment is being considered. While testing of tumor tissue is preferred, cell-free DNA testing can be considered if tumor tissue testing is not feasible (p. PANC-1, PANC-1A, PANC-5, PANC-6A, PANC-9, PANC-10, PANC-11).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Esophageal and Esophagogastric Junction Cancers (3.2025)

This guideline recommends consideration of a liquid biopsy based comprehensive genomic profiling assay in patients who have metastatic or advanced cancer who may be unable to safely undergo a traditional biopsy or when insufficient tumor tissue is available (p. ESOPH-B 6 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends broad molecular profiling for detection of mutations in *RAS*, *BRAF* and other genes along with *HER2* amplifications and MSI during the initial workup or at recurrence in patients with suspected or proven metastatic adenocarcinoma (COL-2,

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COL-9). Testing may be done via blood- or tissue-based NGS panels (COL-B 4 of 10). NCCN recommends consideration of repeat testing after targeted therapy to guide future treatment decisions (p. COL-B, 4 of 10). The NCCN does not recommend molecular profiling via ctDNA for surveillance or de-escalation of care (COL-8, COL-4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline recommends broad-based molecular profiling using ctDNA only when disease is advanced or metastatic adenocarcinoma, large cell, or NSCLC not otherwise specified (NOS). NCCN also recommends consideration of broad molecular profiling for advanced or metastatic squamous cell carcinoma (p. NSCL-19). Per NCCN, "[c]omplete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2) via biopsy and/or plasma testing" are recommended either on tissue, plasma, or both (p. NSCL-20). Both tissue and ctDNA testing have false negative rates and NCCN recommends consideration of complementary testing to increase the likelihood of mutation detection and reduce time to results (p. NSCL-19, NSCL-H, 8 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Cutaneous Melanoma (2.2025)

This guideline supports the use of cell-free circulating tumor DNA (ctDNA) if tumor tissue is unavailable (p. ME-C 3 of 8). In individuals with initial presentation in stage IV disease, broad genomic profiling using larger NGS panels is recommended if feasible, "especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial" (ME-C 4 of 8). If *BRAF* single-gene testing was already done and was negative, NCCN recommends consideration of a larger profiling panel to identify other potential biomarkers (p. ME-C 4 of 8). NCCN recommends tissue testing if testing via ctDNA is negative due to the risk of false negatives (ME-C 3 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

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National Comprehensive Cancer Network (NCCN): Ampullary Adenocarcinoma (2.2025)

This guideline recommends somatic molecular profiling for patients with locally advanced or metastatic disease when systemic therapy is being considered. Testing on tumor tissue is preferred but cell-free DNA testing can be considered if tumor tissue testing is not feasible (p. MS-5, AMP-3, AMP-6, AMP-7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf

National Comprehensive Cancer Network (NCCN): Cervical Cancer (4.2025)

This guideline recommends consideration of comprehensive molecular profiling for cervical cancer that is persistent or recurrent after treatment. If biopsy of the metastatic site is not feasible or if no tissue is available, testing can be done on circulating tumor DNA (p. CERV-10).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

National Comprehensive Cancer Network (NCCN): Biliary Tract Cancers (1.2025)

This guideline recommends comprehensive molecular profiling for patients with unresectable or metastatic biliary tract cancer who are candidates for when systemic therapy is an option. NCCN recommends consideration of a cell-free DNA test if there is not enough tissue available or repeat biopsy cannot be done (p. BIL-B, 1 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Biliary Tract Cancers 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf

National Comprehensive Cancer Network (NCCN): Histiocytic Neoplasms (1.2025)

This guideline mentions molecular testing in the workup for histiocytosis and states that if biopsy is not possible due to location or risk factors, mutational analysis of peripheral blood is an option (p. LCH-1A, ECD-1A).

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National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf

National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors (2.2025)

This guideline recommends consideration of tumor molecular profiling for patients with locoregional unresectable/metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm, pheochromocytoma/paraganglioma, and atypical carcinoid neoplasms when systemic therapy is being considered (NET-6, NET-11, NET-12, WDG3-1, PHEO-1). Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible (p. PDNEC-1, PDNEC-1A).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

National Comprehensive Cancer Network (NCCN): Occult Primary (2.2025)

This guideline recommends consideration of molecular profiling of tumor tissue after an initial determination of histology has been made. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible (p. OCC-1A, OCC-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf

National Comprehensive Cancer Network (NCCN): Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (3.2025)

This guideline recommends somatic testing for *BRCA1/2* and homologous recombination deficiency status for patients at diagnosis and broader molecular testing in the recurrence setting, especially for less common histologies with limited approved treatment options. Testing may be performed on circulating tumor DNA (ctDNA or liquid biopsy) when tissue-based analysis is not clinically feasible (p. OV-B, 1 of 3).

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National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline recommends the use of comprehensive somatic profiling for patients with stage IV or recurrent invasive breast cancer to identify candidates for additional targeted therapies (BINV-18, BINV-Q 6 of 15). Biomarker testing should be done on at least the first recurrence, and either tissue or plasma based assays can be used, and testing of an alternate specimen can be considered if one is negative for actionable biomarkers (p. BINV-18).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

DEFINITIONS

1. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic): 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.
2. **Circulating tumor DNA (ctDNA)** is fragmented, tumor-derived DNA circulating in the bloodstream that is not being carried in a cell. ctDNA derives either directly from the tumor or from circulating tumor cells.

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