

Medical Policy Manual **Draft New Policy: Do Not Implement**

Circulating Tumor DNA (Liquid Biopsy)

DESCRIPTION

Liquid biopsy (e.g., FoundationOne® Liquid CDx, Guardant360®) refers to the analysis of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) as a method of noninvasively characterizing tumors and tumor genome from the peripheral blood. This method may be used to test for single genes or multiple genes using a panel.

Both malignant and nonmalignant cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor or metastases. Analysis of circulating tumor DNA allows multiple samples of blood to be analyzed over time to monitor the molecular changes taking place in a tumor and possibly determining sensitivity to certain treatments.

POLICY

- Circulating tumor DNA (liquid biopsy) companion diagnostic assays are considered **medically necessary** if the medical appropriateness criteria are met. **(See Medical Appropriateness below.)**

MEDICAL APPROPRIATENESS

- Circulating tumor DNA (liquid biopsy) companion diagnostic assays to guide in prescribing certain medications is considered **medically appropriate** when **ALL** of the following are met:
 - Diagnosis of advanced or metastatic cancer (solid tumors)
 - Treatment with a medication in which there is a liquid biopsy-based FDA- approved (e.g., FoundationOne Liquid CDx®, Guardant360® CDx) companion diagnostic being considered
 - FDA label for the drug and indication being considered states companion diagnostic testing is necessary
 - Individuals have not had previous somatic tumor testing to identify genetic changes required to prescribe medication

IMPORTANT REMINDERS

- Any specific products referenced in this policy are just examples and are intended for illustrative purposes only. It is not intended to be a recommendation of one product over another and is not intended to represent a complete listing of all products available. These examples are contained in the parenthetical e.g., statement.
- We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the medical policy and a health plan or government program (e.g., TennCare), the express terms of the health plan or government program will govern.

ADDITIONAL INFORMATION

For guidance on testing criteria, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (<https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools>) for an updated list of FDA-approved tumor markers.

SOURCES

Medical Policy Manual **Draft New Policy: Do Not Implement**

BlueCross BlueShield Association. Evidence Positioning System. (12:2024). *Somatic biomarker testing (including liquid biopsy) for targeted treatment in non-small-cell lung cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, NTRK)*. (2.04.45). Retrieved February 25, 2025 from <https://www.bcbsaoca.com/eps/>. (57 articles and/or guidelines reviewed)

BlueCross BlueShield Association. Evidence Positioning System. (1:2025). *Germline and somatic biomarker testing (including liquid biopsy) for targeted treatment in breast cancer (brca1, brca2, pik3ca, ki-67, ret, braf, esr1, ntrk)*. (2.04.151). Retrieved February 25, 2025 from <https://www.bcbsaoca.com/eps/>. (74 articles and/or guidelines reviewed)

BlueCross BlueShield Association. Evidence Positioning System. (10:2024). *Germline and somatic biomarker testing (including liquid biopsy) for targeted treatment in prostate cancer (brca1/2, homologous recombination repair gene alterations, ntrk gene fusion)*. (2.04.155). Retrieved February 25, 2025 from <https://www.bcbsaoca.com/eps/>. (18 articles and/or guidelines reviewed)

BlueCross BlueShield Association. Evidence Positioning System. (10:2024). *Germline and somatic biomarker testing (including liquid biopsy) for targeted treatment in ovarian cancer (brca1, brca2, homologous recombination deficiency, ntrk)*. (2.04.156). Retrieved February 25, 2025 from <https://www.bcbsaoca.com/eps/>. (23 articles and/or guidelines reviewed)

CMS.gov: Centers for Medicare & Medicaid Services. Palmetto GBA. (2021, December). *MolDX: plasma-based genomic profiling in solid tumors. (LCD ID L38043)*. Retrieved February 25, 2025 from www.cms.gov.

Gouton, E., Malissen, N., Andre, N., Jeanson, A., Pelletier, A., Testot-Ferry, A., et al. (2022). Clinical impact of high throughput sequencing on liquid biopsy in advanced solid cancer. *Current Oncology*, 29 (3), 1902-1918. (Level 4 evidence)

Isla, D., Alvarez, R., Arnal, M., Arriola, E., Azkarate, A, Azkona, E., et al. (2024). Detection of genomic alterations in liquid biopsies from patients with non-small cell lung cancer using foundationone liquid cdx: a cost-effectiveness analysis. (2024). *Journal of Medical Economics*, 27 (1), 1379-1387. (Level 4 evidence)

Mata, D.A., Lee, J.K., Shanmugam, V., Marcus, C.B., Schrock, A.B., Williams, E.A., et al. (2024). Liquid biopsy-based circulating tumour (ct)DNA analysis of a spectrum of myeloid and lymphoid malignancies yields clinically actionable results. *Histopathology*, 84 (7), 1224-1237. Abstract retrieved February 26, 2025 from PubMed database.

National Comprehensive Cancer Network (2025, January). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) *Breast cancer V1.2025*. Retrieved February 25, 2025 from the National Comprehensive Cancer Network

National Comprehensive Cancer Network (2025, January). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) *Non-small cell lung cancer V3.2025*. Retrieved February 25, 2025 from the National Comprehensive Cancer Network

National Comprehensive Cancer Network (2024, July). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) *Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. V3.2024*. Retrieved February 25, 2025 from the National Comprehensive Cancer Network

National Comprehensive Cancer Network (2024, December). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) *Prostate cancer V1.2025*. Retrieved February 25, 2025 from the National Comprehensive Cancer Network



Medical Policy Manual **Draft New Policy: Do Not Implement**

Sposito, M., Belluomini, L., Nocini, R., Insolda, J., Scaglione, L.M., Menis, J., et al. (2024). Tissue- and liquid-biopsy based ngs profiling in advanced non-small-cell-lung cancer in a real-world setting: the imminent study. *Frontiers in Oncology*, 14:1436588. Doi: 10.3389/fonc.2024.1436588. (Level 4 evidence)

U.S. Food and Drug Administration. (2022, August). Center for Devices and Radiological Health. 510(k)Premarket Notification Database. P200010 (Guardant360®). Retrieved February 28, 2025 from <http://www.accessdata.fda.gov>.

U.S. Food and Drug Administration. (2021, July). Center for Devices and Radiological Health. 510(k)Premarket Notification Database. P190032 (FoundationOne® Liquid CDx). Retrieved February 21, 2025 from <http://www.accessdata.fda.gov>.

Woodhouse, R., Li, M., Hughes, J., Delfosse, D., Skoletsky, J., Ma, P., et al. (2020). Clinical and analytical validation of foundationone liquid cdx, a novel 324-gene cfdna-based comprehensive genomic profiling assay for cancers of solid tumor origin. *PLoS One*, 15 (9), e0237802.doi: 10.1371. (Level 2 evidence)

EFFECTIVE DATE

ID_BT