

Background

The term “**liquid biopsy**” encompasses various tests that analyze tumor-derived material in body fluids and serve different purposes in cancer screening, diagnosis and treatment. Broadly speaking, the term is commonly applied to the following blood-based tests:

1. **Multi-cancer early detection (MCED) tests** — Also called multi-cancer detection (MCD) tests. A positive result is often non-specific and may indicate the likelihood that there is cancer somewhere in the body.
2. **Cancer biomarker tests that identify targetable genomic alterations** — These test results may guide treatment decisions as companion diagnostics and identify patients who are likely to respond to certain gene-specific targeted therapies. May be called circulating tumor DNA (ctDNA) or cell-free DNA (cfDNA) tests.
3. **Tests designed to monitor disease progression or identify measurable residual disease (MRD)** — Some tests detect circulating tumor cells while others identify cancer-specific proteins, DNA, or RNA.



The following tips have been developed to support the multidisciplinary cancer care team in understanding when and how to incorporate different liquid biopsy tests.



Clarify the Meaning of “Liquid Biopsy”

Using the same term to describe different types of tests can cause confusion. When using the term “liquid biopsy,” be clear about the type of test and clinical application by considering the following questions:

- ➔ What does the test detect? Circulating tumor cells? Cancer-specific proteins? DNA? RNA?
- ➔ Why is the test being performed? Is the test designed to detect cancer? Or is the test looking for targetable genomic alterations in patients diagnosed with cancer?
- ➔ How will the results impact clinical decisions?

Liquid Biopsy: Early Detection and Screening



Stay Informed about MCED Tests

A 2024 review article found that MCED test sensitivities range from 27% to 95% and differ by organ system.¹ While MCED tests appear promising, there remain unanswered questions about their efficacy, effectiveness, and clinical utility. MCED tests are commercially available, but the Centers for Medicare & Medicaid Services and many health insurance companies do not provide coverage. No professional medical societies nor the US Preventive Services Task Force (USPSTF) have issued recommendations on the use of MCED tests for cancer screening.

The National Cancer Institute (NCI) has created the Cancer Screening Research Network (CSRN) to evaluate new technologies like MCED tests. The CSRN Vanguard Study on Multi-Cancer Detection will enroll up to 24,000 people to explore the feasibility of using MCED tests in clinical trials.² Identify resources like the CSRN website to follow key updates about MCED tests.³



Be Prepared to Speak with Patients about MCED Tests

Cancer clinicians may encounter patients who receive a positive MCED test and seek diagnostic testing. Shared decision-making conversations are needed so that patients understand the role and limitations of diagnostic imaging, invasive biopsies, and other tests. The NCI has a “Questions and Answers about MCD Tests” page that may help cancer clinicians navigate the challenging questions patients may ask regarding their test results.⁴

Liquid Biopsy: Companion Diagnostics and Targeted Therapy Selection

TIP



Consider Complementary or Concurrent Testing: Tissue and Blood

The terms “complementary” and “concurrent” biomarker testing refer to the combined use of both tissue biomarker testing and liquid biopsy to identify targetable genomic alterations in patients with cancer.⁵ Studies are showing that this approach identifies more patients with targetable genomic alterations than by tissue testing alone.⁶ The potential advantages of simultaneous liquid and tissue biopsies include shorter time to obtain a definitive molecular diagnosis, reduced need for a repeat biopsy, and improved detection of actionable mutations.⁷

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer (NSCLC) indicate, “data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection.”⁸

If tissue-based testing includes a limited number of genes (eg, not inclusive of all actionable gene targets), a liquid biopsy may complement the tissue-based test by including additional markers. Alternatively, the tissue-based test may be used to detect protein expression by immunohistochemistry (eg, PD-L1 or HER2) while the liquid biopsy may identify actionable genomic alterations. Weigh the pros/cons when considering this approach.



Note: Insurance companies may not cover a liquid biopsy if the patient is also receiving tissue testing since they may consider this duplicate testing (unless reported as “quantity not sufficient”). Therefore, it is advisable to verify coverage limitations prior to test ordering.

TIP



Order Liquid Biopsy When Tissue Indicates Quantity is Not Sufficient

Diagnostic needle biopsies often yield very limited amounts of tissue, so there may not be enough remaining after primary diagnosis for comprehensive biomarker testing. When pathology indicates that the quantity is not sufficient for testing, consider ordering a liquid biopsy to look for actionable genomic alterations.



Current liquid biopsies do not detect PD-L1 expression, so prioritize the use of tissue for PD-L1 testing when indicated.

TIP



Consider Ordering Liquid Biopsy When Rapid Results are Required

The turnaround time for some liquid biopsies may be less than 7 days while some multigene NGS tissue tests may take over 2 weeks.⁹ In 2022, the European Society for Medical Oncology (ESMO) Precision Medicine Workgroup published recommendations on the use of liquid biopsy.¹⁰ The authors wrote, “Tissue-based testing remains the preferred test for many cancer patients... ctDNA assays may be routinely used when faster results will be clinically important, or when tissue biopsies are not possible or inappropriate.”

TIP



Consider Using Liquid Biopsy to Find Specific Alterations in Other Common Cancers

While non-small cell lung cancer has a long list of actionable genomic alterations, other common cancers may have a limited number of potential targets. Liquid biopsy may be an efficient way to see if certain patients have one or two actionable targets. Consider the following examples where liquid biopsy companion diagnostic testing may identify patients who are eligible for targeted therapies:

- ➔ *BRCA1* and *BRCA2* in ovarian or prostate cancer
- ➔ *BRCA1*, *BRCA2*, and *ATM* in prostate cancer
- ➔ *PIK3CA* and *ESR1* in breast cancer

The NCCN Guidelines® for Occult Primary also recommend considering molecular profiling and while tumor testing is preferred, liquid biopsy can be considered if tumor tissue testing is not feasible.¹¹

TIP



Consider Using Liquid Biopsy to Find Uncommon but Targetable Genomic Alterations

Liquid biopsy may be used to identify *NTRK1/2/3* fusions in patients with solid tumors.¹² They can also detect *RET* fusions in patients with solid tumors.¹³ Patients with solid tumors who have these gene fusions may benefit from targeted therapy.

Liquid Biopsy: Treatment Monitoring

TIP



Identify Treatment-Resistance Mutations

Liquid biopsy may be used when oncologists suspect that a resistance mutation is affecting treatment response. For example, a liquid biopsy may identify a *T790M* mutation on a patient with non-small cell lung cancer receiving a targeted therapy for an *EGFR* mutation.¹⁴ Or, the detection of an *ESR1* mutation in *HR*-positive breast cancer may indicate the patient is resistant to hormone therapy.¹⁵

TIP



Detect Minimal Residual Disease

Certain liquid biopsy tests may be used to detect minimal residual disease (MRD) in patients before any signs of clinically detectable metastatic disease. Tests that detect circulating tumor cells may indicate occult micrometastases that remain undetectable.¹⁶ Ongoing research is demonstrating that MRD testing may improve risk stratification methods and allow clinicians to better predict disease recurrence.¹⁷ Certain MRD tests for specific types of cancers are commercially available and covered by insurance plans, so check before ordering.

Other Considerations

TIP



Review When and How Liquid Biopsies are Ordered

While many cancer programs do not have formal institutional policies concerning the use of liquid biopsy, consider developing a policy and/or reviewing when and how liquid biopsies are ordered to explore the following:

- ➔ Which reference labs perform liquid biopsy?
- ➔ Do all the oncologists and multidisciplinary care team members know when and how to order liquid biopsy?
- ➔ How does this impact turnaround time to treatment?
- ➔ How are patients educated about the tests they receive?
- ➔ Would comprehensive genomic profiling provide more treatment options for this patient?

TIP



Educate Staff About Liquid Biopsy

Given that the term “liquid biopsy” refers to different types of tests, educate staff so they understand the different types of tests and clinical applications. People may get confused about which tests are covered by insurance and when and how different liquid biopsy tests may be used.

TIP



Evaluate the Performance Characteristics of Different Liquid Biopsy Tests

Partner with pathologists who can help oncologists understand and evaluate the performance characteristics of different liquid biopsy tests to determine how they should be used in clinical practice. As new tests become available, it will become increasingly important to understand the science and review the latest evidence to evaluate the benefits and potential limitations of different liquid biopsies.

REFERENCES:

1. Rubinstein WS, Patriotis C, Dickherber A, et al. Cancer screening with multicancer detection tests: A translational science review. *CA Cancer J Clin*. 2024;74(4):368-382. doi:10.3322/caac.21833
2. National Institutes of Health. NIH launches research network to evaluate emerging cancer screening technologies. nih.gov/news-events/news-releases/nih-launches-research-network-evaluate-emerging-cancer-screening-technologies
3. U.S. Department of Health and Human Services. NIH launches research network to evaluate emerging cancer screening technologies. cancer.gov/news-events/press-releases/2024/cancer-screening-research-network-launches
4. U.S. Department of Health and Human Services. Questions and Answers about MCD Tests. prevention.cancer.gov/major-programs/multi-cancer-detection-mcd-research/questions-and-answers-about-mcd-tests
5. Desmeules P, Dusselier M, Bouffard C, et al. Retrospective assessment of complementary liquid biopsy on tissue single-gene testing for tumor genotyping in advanced NSCLC. *Curr Oncol*. 2023;30(1):575-585. doi:10.3390/curroncol30010045
6. Iams WT, Mackay M, Ben-Shachar R, et al. Concurrent Tissue and Circulating Tumor DNA Molecular Profiling to Detect Guideline-Based Targeted Mutations in a Multicancer Cohort. *JAMA Netw Open*. 2024;7(1):e2351700. Published 2024 Jan 2. doi:10.1001/jamanetworkopen.2023.51700
7. Maity AP, Gangireddy M, Degen KC, et al. Impact of Simultaneous Circulating Tumor DNA and Tissue Genotyping in the Workup of Stage IV Lung Adenocarcinoma on Quality of Care in an Academic Community Medical Center. *JCO Oncol Pract*. 2023;19(8):620-625. doi:10.1200/OP.22.00405
8. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.11.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed October 20, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
9. Pennell NA, Arcila ME, Gandara DR, West H. Biomarker Testing for Patients With Advanced Non-Small Cell Lung Cancer: Real-World Issues and Tough Choices. *Am Soc Clin Oncol Educ Book*. 2019 Jan;39:531-542. doi: 10.1200/EDBK_237863. Epub 2019 May 17. PMID: 31099633.
10. Pascual J, Attard G, Bidard FC, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. *Ann Oncol*. 2022;33(8):750-768. doi:10.1016/j.annonc.2022.05.520
11. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Occult Primary. V.2.2025. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed September 15, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
12. Chakravarty D, Johnson A, Sklar J, et al. Somatic genomic testing in patients with metastatic or advanced cancer: ASCO provisional clinical opinion [published correction appears in *J Clin Oncol*. 2022;40(18):2068]. *J Clin Oncol*. 2022;40(11):1231-1258. doi:10.1200/JCO.21.02767
13. Parimi V, Tolba K, Danziger N, et al. Genomic landscape of 891 RET fusions detected across diverse solid tumor types. *NPJ Precis Oncol*. 2023;7(1):10. Published 2023 Jan 23. doi:10.1038/s41698-023-00347-2
14. Hochmair MJ, Buder A, Schwab S, et al. Liquid-biopsy-based identification of EGFR T790M mutation-mediated resistance to afatinib treatment in patients with advanced EGFR mutation-positive NSCLC, and subsequent response to osimertinib. *Target Oncol*. 2019;14(1):75-83. doi:10.1007/s11523-018-0612-z
15. Dustin D, Gu G, Fuqua SAW. ESR1 mutations in breast cancer. *Cancer*. 2019 Nov 1;125(21):3714-3728. doi: 10.1002/cncr.32345. Epub 2019 Jul 18. PMID: 31318440; PMCID: PMC6788940.
16. Feng Z, Wu J, Lu Y, et al. Circulating tumor cells in the early detection of human cancers. *Int J Biol Sci*. 2022;18(8):3251-3265. Published 2022 May 1. doi:10.7150/ijbs.71768
17. Zheng J, Qin C, Wang Q, Tian D, Chen Z. Circulating tumour DNA-Based molecular residual disease detection in resectable cancers: a systematic review and meta-analysis. *EBioMedicine*. 2024;103:105109. doi:10.1016/j.ebiom.2024.105109

In partnership with:



Explore additional precision medicine resources at accancer.org/cancer-diagnostics.

Supported by:



The **Association of Cancer Care Centers (ACCC)** is the leading education and advocacy organization for the cancer care community. For more information, visit accancer.org.

© 2024. Association of Cancer Care Centers. All rights reserved.