BACKGROUND

In 2020, the US Food and Drug Administration (FDA) approved the first set of liquid biopsy companion diagnostic tests for patients with advanced cancers who may be eligible for targeted therapy. Since then, a host of liquid biopsy tests have emerged. While the phrase “liquid biopsy” may refer to different types of tests, this tip sheet refers to plasma-based tests used to identify gene targets in patients with known cancer.

The terms complementary and concurrent testing are emerging in reference to the combined use of both tissue biomarker testing and liquid biopsy. In some instances, liquid biopsy is performed only when tissue test results are incomplete (e.g., tissue is reported as “quantity not sufficient” (QNS) or when tissue testing only includes a limited number of genes (e.g., a panel of genes that does not include uncommon or investigational targets). In other cases, both tissue and liquid testing may be ordered and performed at the same time. These terms are not always clearly defined in the literature and payers do not appear to have a uniform coverage policy regarding complementary or concurrent testing. Some 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 QNS). Therefore, it is advisable to verify coverage limitations prior to test ordering.

The following tips have been developed to support the multidisciplinary cancer care team in understanding how to optimize the role of liquid biopsy.

LIQUID BIOLOGY: a test that enables the analysis of tumors using a blood sample alone. It may also be called cell-free DNA (cfDNA) or circulating tumor DNA (ctDNA) tests. Liquid biopsy is performed using next-generation sequencing (NGS) and some experimental liquid biopsies are incorporating RNA-based testing.

Consider Complementary or Concurrent Testing: Tissue and Blood

If a tissue-based test includes a limited number of genes (e.g., 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 (e.g., PD-L1) while the liquid biopsy may identify actionable genomic alterations. Weigh the pros/cons when considering this approach.

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.” The IASLC consensus statement states that liquid biopsy is a rapidly evolving field and that newer NGS approaches are leading to improved sensitivity and specificity.

Order Liquid Biopsy When Tissue Indicates Quantity Not Sufficient (QNS)

Diagnostic needle biopsies often yield very limited amounts of tissue, so there may not be enough tissue remaining after primary diagnosis for comprehensive biomarker testing. When pathology indicates QNS for testing, consider ordering a liquid biopsy to look for actionable genomic alterations. Since some patients may be medically unfit for invasive tissue sample, a liquid biopsy may be used to identify potential gene targets.

Current liquid biopsies do not detect PD-L1 expression, so prioritize the use of tissue for PD-L1 testing when indicated.
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 1 or 2 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® recommend considering molecular profiling for patients who are candidates for anti-cancer therapy to identify uncommon mutations. While tumor testing is preferred, cell-free DNA testing can be considered if tumor tissue testing is not feasible.

Liquid biopsy may be used when oncologists suspect that a resistance mutation may be 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.

Liquid biopsy has the advantage of being noninvasive and may be most beneficial when tissue is unavailable or when patients are unable to undergo a new biopsy. Liquid biopsy may be used to identify rare alterations such as NTRK1/2/3 fusions. While liquid biopsy is fast and convenient, most do not test for RNA, so tissue testing using RNA-based approaches remains the best method for identifying gene fusions. Patients with solid tumors who have rare alterations such as NTRK or RET gene fusions may benefit from targeted therapy.

While many cancer programs do not have formal institutional policies around 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 complimentary or concurrent testing with liquid biopsy provide more treatment options for this patient?
Learn more: accc-cancer.org/cancer-diagnostics.

**REFERENCES:**


3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.1.2024.  © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed December 21, 2023. 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.


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