

Commentary

CSF Liquid Biopsy: From Spinal Tap to Molecular Map

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Received date: August 23, 2026; **Accepted date:** August 28, 2026; **Published date:** September 16, 2026

Citation: Edina Komlodi-Pasztor (2026) CSF Liquid Biopsy: From Spinal Tap to Molecular Map. J Clin Trial Case Stud, 9:2.

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About the study

Cerebrospinal Fluid Liquid Biopsy (CSF LBx) is an emerging and evolving tool in the evaluation of Central Nervous System (CNS) lesions. Although tissue diagnosis remains the gold standard for the diagnosis and classification of CNS malignancies, the detection of circulating tumor DNA (ctDNA) in Cerebrospinal Fluid (CSF) provides a new approach to identifying, characterizing and monitoring a neoplastic disease. In selected clinical situations, the molecular information gained from CSF LBx may also help guide treatment decisions.

Liquid biopsy is not a new concept in medicine. It refers to the analysis of biological fluids (such as blood, urine, sputum, or CSF) for cellular or molecular markers of a disease. In oncology, liquid biopsy approaches have been used for many years, including urine-based testing for bladder cancer and blood-based circulating tumor DNA assays for solid tumors and lymphoma [1-3]. The development of increasingly sensitive molecular technologies has expanded this concept to CSF. Historically, CSF analysis for suspected CNS malignancy has relied primarily on cytology and later on the addition of flow cytometry. These approaches remain valuable, particularly for the detection of (primary) CNS lymphoma, but their sensitivity can be limited by low numbers of circulating tumor cells, the need for adequate CSF volume, and the requirement for rapid processing. CSF LBx represents a shift from cell-based analysis toward detection of circulating tumor DNA. CSF LBx analyzes DNA fragments released by the tumor into the CSF and can potentially provide molecular information from lesions located throughout the neuraxis, including supratentorial, infratentorial, and spinal lesions. This approach is particularly relevant when malignancy is included in the differential diagnosis of a CNS lesion.

For patients with a suspected primary brain tumor, CSF LBx should generally be viewed as an ancillary test rather than a replacement for tissue diagnosis. It may be particularly useful when only a small biopsy can be safely obtained and the available tissue may be insufficient for the increasingly extensive immunohistochemical and molecular testing required for modern tumor classification [4]. CSF LBx may also be considered when surgical biopsy or resection carries substantial morbidity. This can include selected deep-seated lesions, lesions in surgically challenging locations, or spinal lesions for which tissue acquisition may carry significant neurological risk [5]. In these situations, CSF LBx may provide molecular information that would otherwise be difficult or impossible to obtain. The potential clinical value of molecular information is substantial. Molecular alterations can influence tumor classification and alter treatment recommendations. For example, identification of a defining alteration in a CNS tumor may help establish or refine the diagnosis and potentially identify an actionable therapeutic target.

CSF LBx may also have an important role in patients with suspected metastatic or leptomeningeal disease. Molecular analysis of CSF has the potential to establish the presence of tumor-derived DNA and provide insight into the molecular characteristics of CNS disease, particularly when the origin of a CNS lesion is uncertain or when there is concern for a second primary malignancy. CSF LBx may be particularly useful in the evaluation of Leptomeningeal Disease (LMD) [6]. In patients with equivocal imaging findings, detection of tumor-derived ctDNA in CSF may provide additional evidence supporting CNS dissemination. This application is especially relevant because LMD can be challenging to diagnose using imaging and conventional CSF studies alone. Beyond diagnosis and molecular characterization, CSF LBx is also being investigated as a tool for monitoring treatment response and disease evolution. Serial assessment of tumor-derived ctDNA may eventually provide a dynamic measure of tumor burden or molecular changes during treatment. However, the clinical utility of serial CSF LBx and its ability to reliably predict treatment response or progression have not yet been proven and remain areas of ongoing investigation.

Despite its promise, CSF LBx remains an evolving technology, and appropriate expectations are essential. A negative result does not necessarily exclude a CNS malignancy. Tumor DNA shedding into the CSF may be variable and can depend on tumor location, tumor burden, biological characteristics, and the relationship of the lesion to the CSF space. Therefore, in a patient with an undiagnosed CNS lesion, a negative CSF LBx may represent either the absence of detectable tumor DNA or a false-negative result. Similarly, a positive molecular result

must always be interpreted in the context of the clinical and radiographic findings. Occasionally, molecular findings may be difficult to reconcile with the clinical presentation or imaging and may not fully explain the underlying lesion. CSF LBx should therefore not be interpreted in isolation.

At the same time, when appropriately used, CSF LBx can provide valuable information. It may help identify neoplasia, provide molecular characterization, and guide treatment across primary CNS tumors, metastatic disease, and leptomeningeal disease. What began decades ago with CSF cytology and subsequently expanded to flow cytometry has now progressed to molecular analysis of circulating tumor DNA. Importantly, CSF LBx does not eliminate the value of tissue diagnosis. Rather, it provides an additional source of information that can complement tissue-based diagnosis, particularly when tissue is limited, inaccessible, or associated with substantial procedural risk.

The clinical value of this technology has been increasingly recognized. Liquid biopsy was first introduced into the NCCN Guidelines in 2023 as a diagnostic tool for Leptomeningeal Disease (LMD). In 2025, its recommended use was further expanded to include the detection of primary CNS lymphoma, ependymoma, and medulloblastoma. In 2026, the guidelines expanded recommendations for CSF ctDNA testing to biopsy-infeasible cases with high clinical suspicion for high-grade glioma or glioblastoma, as well as H3K27-altered tumors, where it may aid diagnosis, molecular characterization, and assessment of treatment response [5]. As technology continues to improve, greater sensitivity, broader molecular profiling, and better understanding of tumor DNA shedding may further expand its clinical utility. Future developments might extend the assay to incorporate RNA and protein-based approaches to further enhance the clinical utility of the test. For now, CSF LBx should be viewed as a promising complementary tool in neuro-oncology, one that can provide meaningful molecular insight while requiring careful interpretation within the broader clinical context.

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