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Circulating tumor DNA as a liquid biopsy for glioma detection in cerebrospinal fluid and plasma: A systematic review and meta-analysis

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Abstract

Introduction. Accurate molecular characterization of gliomas is essential for determining prognosis and guiding therapeutic decisions. In recent years, liquid biopsy for analysis of circulating tumor DNA (ctDNA) in blood or cerebrospinal fluid (CSF) has emerged as a promising, minimally invasive alternative. This study evaluates the existing literature on the utility of ctDNA detection in CSF and blood in patients with gliomas, with the goal of assessing its ability to identify mutations concordant with those detected in tumor tissue.

Methods. A systematic search was conducted up to April 30, 2026, to identify cohorts that evaluated the effectiveness of ctDNA-based liquid biopsies for gliomas. The primary assessed outcomes were the sensitivity and specificity of the liquid biopsies using CSF or plasma. A pooled sensitivity analysis was performed, as well as summary receiver operating characteristic (SROC) curves.

Results. Twenty-eight studies met the inclusion criteria, encompassing 613 patients. Meta-analysis of diagnostic performance revealed improved biomarker performance for CSF (Area under the curve [AUC] 0.95) ctDNA. Pooled sensitivity for ctDNA detection in patients with gliomas was higher in CSF 0.79 (95% CI, 0.69-0.85) than in plasma 0.29 (95% CI, 0.15-0.47), $P < .0001$.

Conclusion. The literature demonstrates a promising performance of ctDNA analysis in patients with diffuse gliomas as a liquid biopsy strategy. CSF ctDNA analysis exhibited superior sensitivity compared to plasma ctDNA. This meta-analysis supports the utility of ctDNA, particularly CSF ctDNA, as a complementary diagnostic tool in neuro-oncology.

Key Points

- Promising performance of ctDNA analysis in patients with gliomas as a liquid biopsy strategy.
- CSF ctDNA analysis exhibited superior sensitivity compared to plasma ctDNA.

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Importance of the Study

The purpose of this review is to evaluate the clinical utility of circulating tumor DNA (ctDNA) detection in plasma and cerebrospinal fluid (CSF) for identifying tumor-associated molecular alterations in adults with intracranial gliomas. Our findings demonstrate that CSF-derived ctDNA has substantially higher sensitivity than plasma-derived ctDNA, while both show high specificity for the detection of tumor-concordant mutations. These results support the potential role of ctDNA as a complementary molecular tool in glioma evaluation, particularly when tumor tissue is limited or difficult to obtain. However, important clinical and methodological heterogeneity across studies, including differences in tumor classification, treatment status, assay platforms, and sample processing, limits the generalizability of the pooled estimates. Future studies using standardized protocols and WHO CNS5-based tumor classification are needed to define the optimal clinical applications of ctDNA and determine its prognostic and therapeutic relevance.

Gliomas are the most common primary tumors arising within the central nervous system (CNS).[1] They encompass a wide spectrum of neoplasms developing from a variety of glial cells and may either be benign or malignant.[1] The classification of these tumors has evolved significantly from early histopathology-based systems that primarily focused on tumor morphology and histological features such as cellularity, mitotic activity, and necrosis,[2] to the more modern and comprehensive framework established by the World Health Organization (WHO) that also incorporates molecular features.[3] Furthermore, this molecular stratification serves as both a powerful diagnostic and prognostic tool.

In gliomas, mutations in the isocitrate dehydrogenase (IDH) represent the initial and most critical branching point, as their presence confers a significantly improved prognosis compared with their IDH-wildtype counterparts. IDH-mutant tumors may be further classified by assessing for the mutually exclusive presence of either combined whole-arm deletion of chromosomes 1p and 19q (a defining feature of oligodendroglioma) or mutations in the transcription regulator alpha thalassemia/mental retardation syndrome X-linked (ATRX) and the tumor suppressor gene, TP53 (characteristic of astrocytoma).[3]

The established gold standard to diagnose, stratify, and stage patients with brain tumors relies on tissue biopsy for histopathology analysis. However, tissue evaluation has significant limitations and risks.[4,5] These risks are particularly pronounced for tumors located in eloquent areas such as the brainstem or thalamus, where a biopsy may represent a high-risk intervention or be entirely unfeasible.[4] Furthermore, due to the well-documented intratumoral heterogeneity of gliomas, a small single tissue sample may not be representative of the tumor's complete molecular landscape, creating a risk of sampling errors that can hamper an accurate diagnosis and limit treatment options.[6] These limitations not only challenge the initial diagnosis but also can preclude the routine use of repeated biopsies or resections for assessment of tumor recurrence and response to therapy.[7,8]

In response to these challenges, liquid biopsy has emerged as a major development with significant translational potential. This strategy, which provides essential genomic information, is predicated on the molecular analysis of tumor-derived material isolated from blood and other body fluids. These analytes include circulating tumor cells (CTCs), extracellular vesicles (EVs), and various circulating nucleic acids, with the analysis of circulating tumor DNA (ctDNA) being the most widely applied technique. This study aims to systematically evaluate the literature regarding the implementation of ctDNA analysis from plasma and cerebrospinal fluid (CSF) in patients with diffuse gliomas.[9]

Methods

Study Design and Registration

The systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[10] The systematic review and meta-analysis were registered a priori in the PROSPERO database (CRD420251064701).

Eligibility Criteria

To be eligible for this study, the selected studies needed to follow the PICO format and satisfy the following inclusion criteria: (1) Studies evaluating adult patients with pathology-confirmed gliomas; (2) Evaluated the detection of ctDNA in CSF and/or blood (serum, plasma, or whole blood) in patients with gliomas; (3) Reported sufficient data such as patient population, type of tumor, patient age, the method for biospecimen analysis, and enough data to calculate the sensitivity and/or specificity accurately; (4) Cohorts and clinical trials that were published in English or Spanish. To ensure the data comprehensively represented gliomas in adults, the following exclusion criteria were applied: (1) Liquid biopsy was not part of the analysis; (2) Samples or subjects had a non-glioma tumor; (3) The tumor was not located intracranially; (4) Tumor tissue was found to contain no mutations; (5) Plasma and CSF with insufficient or undetectable levels of ctDNA for sequencing.

Information Sources and Search Strategy

A systematic search was performed on PubMed, EMBASE, and Cochrane Library databases to identify relevant studies on April 30, 2026. The main terms used for the

search included "glioma," "CSF," "blood," "ctDNA," and "liquid biopsy."

Selection and Data Collection Process

Full-text article screening was performed by 3 individual reviewers, who assessed relevant information such as patient population, age, and type of study. Subsequently, data extraction from the included articles was performed by 7 individual reviewers and supervised by one of the authors. The risk of bias of the selected studies was assessed individually by 3 reviewers based on the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I).[11,12]

Data Measurement and Synthesis

The included studies were analyzed both quantitatively and qualitatively. Sensitivities and specificities of ctDNA detection were either directly extracted from each study's reported results or, when available, calculated from raw data included in the Supplementary Materials. A pooled sensitivity of glioma ctDNA detection was generated for both CSF-based and plasma-based studies. Confidence intervals for each study included in the sensitivity analysis were calculated using the Wilson method, and the results were presented in forest plots.[13] Statistical heterogeneity across studies was evaluated using Cochran's Q test and quantified with the I^2 statistic.[14]

In addition, a subgroup analysis was performed to compare the sensitivities of studies that used Next-Generation Sequencing (NGS) for ctDNA detection in CSF with those that used Digital Droplet PCR (ddPCR). Effect sizes across studies were further examined using meta-regression analyses. Summary receiver operating characteristic (SROC) curves were produced using the Rücker–Schumacher method.[15]

We retrieved basic demographic information, including age at diagnosis, gender, tumor type, and tumor classification according to the 2021 WHO Classification of Tumors of the CNS,[3] and the timing of biospecimen collection for the liquid biopsy. All statistical analyses were conducted using R (version 4.5.2; The R Foundation for Statistical Computing).

Results

The initial literature search yielded a total of 723 articles. After removing 43 duplicates, 680 records were screened for eligibility. Of these, 28 studies met the inclusion criteria and were incorporated into the quantitative analysis, including 27 prospective and 1 retrospective studies. The study selection process is illustrated in the PRISMA flowchart. An overview of the included studies is presented in Table 1.

Among the selected articles, 6 reported sufficient data to calculate sensitivity and specificity for ctDNA in CSF, and 2 for ctDNA in plasma. Consequently, our analysis included 21 single-arm studies and 7 double-arm studies. Seventeen of the included articles analyzed ctDNA using NGS, 2 employed both NGS and ddPCR, and 9 used other PCR-based methods. The overall risk of bias across the included studies was assessed as moderate (Figure 1).

Patient Characteristics

A total of 613 patients were included in this meta-analysis, comprising data from 501 glioma patients and 112 control subjects. All patients were adults aged 18 years or older, and more than 80% of the glioma cases were high-grade tumors.

Diagnostic Accuracy of ctDNA in Plasma and CSF

We conducted a meta-analysis to determine the diagnostic accuracy of ctDNA in plasma and CSF for glioma detection. Using the sensitivity and specificity data from the included records, we generated SROC curves and calculated the area under the curve (AUC). The AUC for ctDNA in CSF was 0.95. It was not possible to perform AUC for ctDNA in plasma due to the small number of studies evaluating plasma ctDNA with sufficient information to calculate specificity. These values suggest that ctDNA in CSF has a high diagnostic accuracy for ctDNA glioma detection Figure 2. The pooled sensitivity for glioma detection using ctDNA in CSF was 0.79 (95% CI, 0.69-0.85), while for plasma, the pooled sensitivity was significantly lower at 0.29 (95% CI, 0.15-0.47), as illustrated in the forest plots in Figure 3. This difference was statistically significant ($P < .0001$). These results indicate that ctDNA in CSF is a more reliable biomarker for glioma diagnosis when compared to ctDNA in plasma. The pooled specificity for CSF was 0.94 (95% CI, 0.84-0.98) and of 0.98 (95% CI, 0.85-1.00) for plasma.

Digital Droplet Polymerase Chain Reaction versus NGS in CSF

The pooled sensitivity of the 4 studies that implemented ddPCR for processing ctDNA in CSF was of 0.72 (95% CI, 0.21-0.95), while for the 16 NGS-based studies it was of 0.82 (95% CI, 0.71-0.88). No statistically significant difference was observed ($P = .58$).

Cerebrospinal Fluid Source

Data on the origin of CSF samples were available for 330 patients; 176 samples were obtained by lumbar puncture (LP), whereas 154 were collected intraoperatively from the ventricular system or subarachnoid space. The pooled sensitivity was 0.75 (95% CI, 0.59-0.86) for LP samples and 0.81 (95% CI, 0.72-0.88) for samples obtained intraoperatively; nevertheless, the difference was not significant ($P = .43$).

Tumor Characteristics and ctDNA Analysis in CSF

When CSF sensitivity was stratified by tumor grade, detection was significantly higher in high-grade tumors than in

Table 1. Summary of studies included in the meta-analysis

Author(s), year, and country	Study design	Population size	Median Age	Type of tumors	Sample	Test for ctDNA analysis	Number of targeted genes	Test accuracy	
								Sensitivity	Specificity
Cerebrospinal fluid and plasma									
De Mattos-Arruda et al. (2015); Spain[16]	Prospective	4	53	GBM (*n*=4)	CSF and plasma	ddPCR	341	CSF: 100% Plasma: 0%	N/A
Juratli et al. (2018); Germany[17]	Prospective	42	67	Glioblastoma (*n*=38), Oligodendroglioma, IDH-mutant, 1p/19q-codeleted (*n*=4)	CSF and plasma	ddPCR	1	CSF: 84% Plasma: 17%	N/A
Pan et al. (2018); China[18]	Prospective	16	42	Astrocytoma WHO grade II (*n*=5), Anaplastic Astrocytoma WHO grade III (*n*=5), Anaplastic Oligoastrocytoma WHO grade III (*n*=1), Ependymoma WHO grade II (*n*=1), Glioblastoma (*n*=3), Subependymoma (*n*=1)	CSF and plasma	NGS	68	CSF: 94% Plasma: 0%	N/A
Li et al. (2019); China[19]	Prospective	5	61	Glioblastoma (*n*=5)	CSF and plasma	NGS	50	CSF: 100% Plasma: 100%	N/A
Orzan et al. (2023); Italy[7]	Prospective	36	66	Glioblastoma (*n*=37), Astrocytoma, IDH-mutant, WHO grade IV (*n*=2), Anaplastic Oligodendroglioma (*n*=1)	CSF and plasma	ddPCR and NGS	54	CSF: 85% Plasma: 43%	N/A
Cabezas-Camareno et al. (2025); Spain[20]	Prospective	17	55	Glioblastoma (*n*=8), Astrocytoma, IDH-mutant (*n*=6), Oligodendroglioma, IDH-mutant (*n*=3)	CSF and Plasma	NGS	8	CSF: 82% Plasma: 50%	N/A
Köpp et al. (2026); Switzerland[21]	Prospective	3	NA	Glioblastoma (*n*=3)	CSF and plasma	NGS	324	CSF: 33% Plasma: 33%	N/A
Cerebrospinal fluid									
Wang et al. (2015); United States[22]	Prospective	10	69	Glioblastoma (*n*=8), Astrocytoma WHO grade III (*n*=1), Pilocytic Astrocytoma (*n*=1)	CSF	NGS	4	89%	N/A
Pentsova et al. (2016); United States[23]	Prospective	7	46	Anaplastic Oligodendroglioma (*n*=3), Glioblastoma (*n*=2), Anaplastic Astrocytoma (*n*=1), Anaplastic Ependymoma (*n*=1)	CSF	NGS	341	57%	N/A
Martínez-Ricarte et al. (2018); Spain[24]	Prospective	20	57	Glioblastoma (*n*=9), Astrocytoma, IDH-mutant, WHO grade IV (*n*=1), Oligodendroglioma (*n*=4), Anaplastic Astrocytoma (*n*=2), Astrocytoma (*n*=1), Diffuse Midline Glioma (*n*=3)	CSF	ddPCR and NGS	7	85%	N/A

Table 1. Continued

Author(s), year, and country	Study design	Population size	Median Age	Type of tumors	Sample	Test for ctDNA analysis	Number of targeted genes	Test accuracy	
								Sensitivity	Specificity
Mouliere et al. (2018); England[25]	Prospective	9	NA	Glioblastoma (*n*=8), Oligodendroglioma (*n*=1)	CSF	NGS	2	56%	N/A
Miller et al. (2019); United States[26]	Retrospective	43	41.5	Anaplastic Astrocytoma, IDH-mutant (*n*=6), Anaplastic Astrocytoma, IDH-wildtype (*n*=2), Astrocytoma, IDH-mutant (*n*=1), Astrocytoma, IDH-wildtype (*n*=1), Anaplastic Oligodendroglioma, IDH-mutant, 1p/19q-codeleted (*n*=2), Oligodendroglioma, IDH-mutant, 1p/19q-codeleted (*n*=3), Glioblastoma (*n*=21)	CSF	NGS	410	97%	100%
Duan et al. (2020); China[27]	Prospective	8	60	Glioblastoma (*n*=7), Astrocytoma, IDH-mutant, WHO grade 4 (*n*=1)	CSF	NGS	27	100%	N/A
Zhao et al. (2020); China[28]	Prospective	17	46	Diffuse Astrocytoma (*n*=6), Anaplastic Oligodendroglioma (*n*=3), Anaplastic Astrocytoma (*n*=4), Glioblastoma (*n*=4)	CSF	NGS	50	87%	N/A
Fujioka et al. (2021); Japan[29]	Prospective	43	N/A	Glioblastoma, IDH-mutant (*n*=5), Glioblastoma, IDH-wildtype (*n*=5), Diffuse Midline Glioma, H3 K27M-mutant (*n*=6), Anaplastic Oligodendroglioma, IDH-mutant (*n*=10), Anaplastic Astrocytoma, IDH-mutant (*n*=3), Anaplastic Astrocytoma, IDH-wildtype (*n*=2), Oligodendroglioma, IDH-mutant (*n*=1), Oligoastrocytoma, IDH-mutant (*n*=1), Diffuse Astrocytoma, IDH-mutant (*n*=2), Diffuse Astrocytoma, IDH-wildtype (*n*=2)	CSF	Digital Chip-based PCR	3	58%	100%
Gupta et al. (2021); United States[30]	Prospective	9	N/A	Glioblastoma (*n*=2)	CSF	Multiplexed Quantitative PCR	5	0%	78%
On et al. (2021); Japan[31]	Prospective	1	23	Diffuse midline glioma (*n*=1)	CSF	ddPCR	1	0%	N/A

Table 1. Continued

Author(s), year, and country	Study design	Population size	Median Age	Type of tumors	Sample	Test for ctDNA analysis	Number of targeted genes	Test accuracy	
								Sensitivity	Specificity
Fujita et al. (2022); United States[32]	Prospective	7	31	Oligodendroglioma, IDH-mutant, WHO grade III (*n*=3), Astrocytoma, IDH-mutant, CNS WHO grade 2 (*n*=1), Astrocytoma, IDH-mutant, CNS WHO grade 4 (*n*=1), Astrocytoma, IDH-mutant, CNS WHO grade 3 (*n*=1)	CSF	ddPCR	1	33%	100%
Hickman et al. (2024); United States[33]	Prospective	38	N/A	Glioblastoma (*n*=20), Diffuse Midline Glioma (*n*=2), Diffuse Hemispheric Glioma (*n*=2), Astrocytoma, IDH-mutant (*n*=6), Oligodendroglioma, IDH-mutant, 1p/19q-codeleted (*n*=3), Optic Pathway Glioma (*n*=2), Pilocytic Astrocytoma (*n*=1), Glioma NOS (*n*=1), High-grade Glioma NOS (*n*=1)	CSF	NGS	129	94%	N/A
Iser et al. (2024); Germany[34]	Prospective	55	59	Glioblastoma (*n*=26), Diffuse Midline Glioma (*n*=2), Oligodendroglioma WHO grade II (*n*=1), Oligodendroglioma WHO grade III (*n*=1), Pilocytic Astrocytoma WHO grade 1 (*n*=1), Ependymoma (*n*=1), Astrocytoma, IDH-mutant, WHO grade IV (*n*=1), Astrocytoma, IDH-mutant, WHO grade II (*n*=1), Glioma NOS (*n*=4)	CSF	NGS	38	54%	100%
Zhu et al. (2025); United States[35]	Prospective	11	45	Astrocytoma (*n*=1), Anaplastic Astrocytoma (*n*=2), Astrocytoma, IDH-mutant, WHO grade IV (*n*=1), Anaplastic Oligodendroglioma (*n*=3), Glioblastoma (*n*=4)	CSF	NGS	68	82%	N/A
Khurana et al. (2026); United States[36]	Prospective	56	NA	Glioma (*n*=8), Astrocytoma (*n*=4), Glioblastoma (*n*=2), Oligodendroglioma (*n*=2)	CSF	NGS	520	94%	98%

Table 1. Continued

Author(s), year, and country	Study design	Population size	Median Age	Type of tumors	Sample	Test for ctDNA analysis	Number of targeted genes	Test accuracy	
								Sensitivity	Specificity
Plasma									
Lavon et al. (2010); Israel[37]	Prospective	90	58	High-grade Astrocytoma (n=41), High-grade Oligodendroglioma (n=14), Low-grade Oligodendroglioma (n=15)	Plasma	Conventional PCR	NA	60%	100%
Boisselier et al. (2012); France[38]	Prospective	15	N/A	IDH-mutant Glioma (n=25), IDH-wildtype Glioma (n=14)	Plasma	COLD-PCR and Digital PCR	1	33%	100%
Salkeni et al. (2015); United States[39]	Prospective	1	N/A	Glioblastoma (n=1)	Plasma	Conventional PCR	1	100%	N/A
Bettegowda et al. (2014); China[40]	Prospective	23	45	Glioblastoma (n=10), Astrocytoma WHO grade II (n=6), Anaplastic Astrocytoma (n=1), Anaplastic Oligodendroglioma (n=6)	Plasma	PCR-ligation and NGS	100	0%	N/A
Sun et al. (2019); China[41]	Prospective	6	51	Glioblastoma (n=4), Anaplastic Oligodendroglioma (n=1), Astrocytoma (n=1)	Plasma	NGS	62	0%	N/A
Bagley et al. (2020); United States[42]	Prospective	17	N/A	Glioblastoma (n=20)	Plasma	NGS	74	6%	N/A

Abbreviations: COLD, co-amplification at lower denaturation temperature; CSF, cerebrospinal fluid; ctDNA, circulating tumor deoxyribonucleic acid; ddPCR, digital droplet polymerase chain reaction; N/A, not available; NGS, next-generation sequencing; PCR, polymerase chain reaction; qPCR, quantitative polymerase chain reaction.

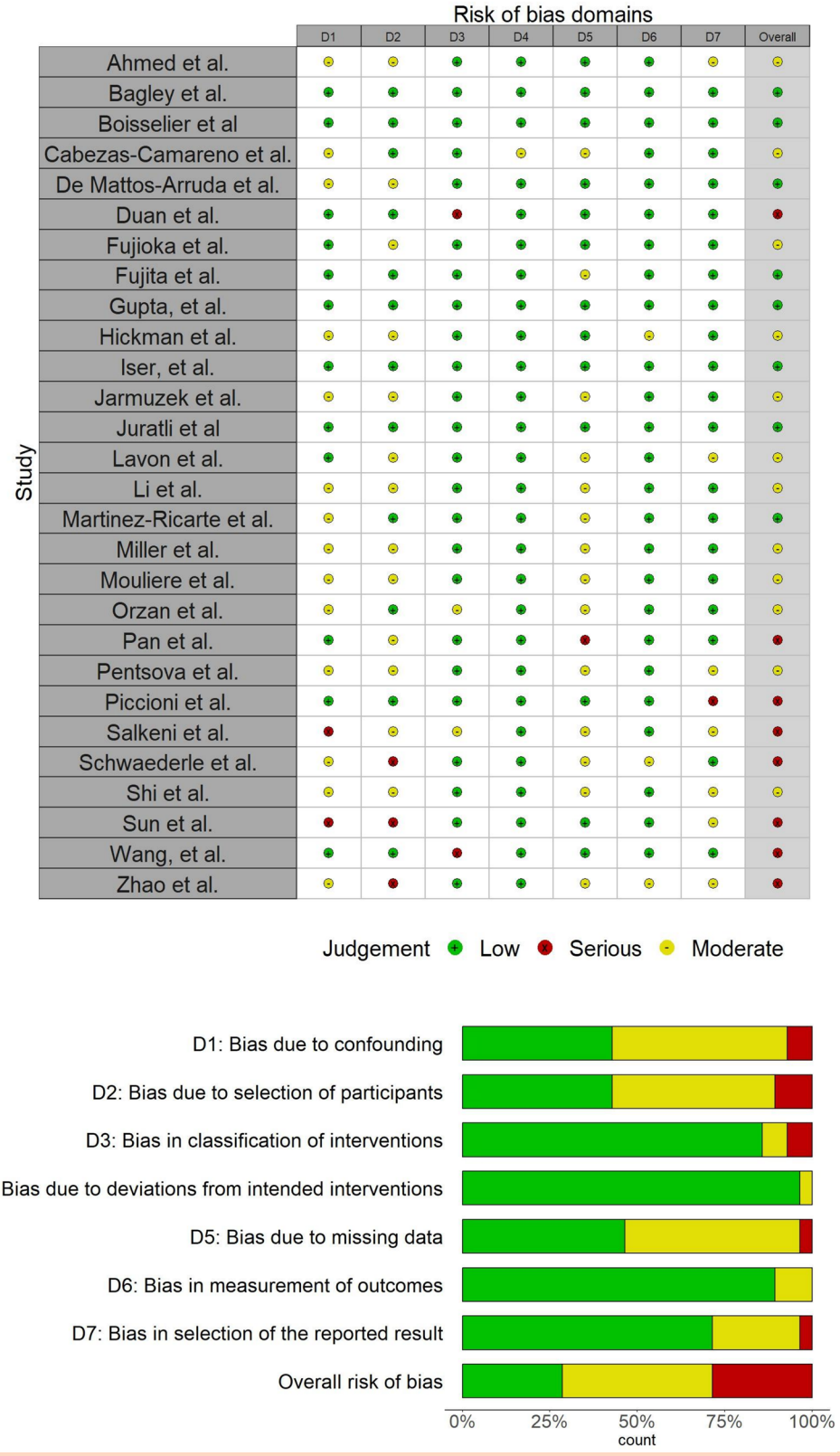


Figure 1. Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) comprehensive figure according to the Cochrane network. Evaluation of the risk of bias of the individual studies included in the systematic review according to the ROBINS-I assessment tool.

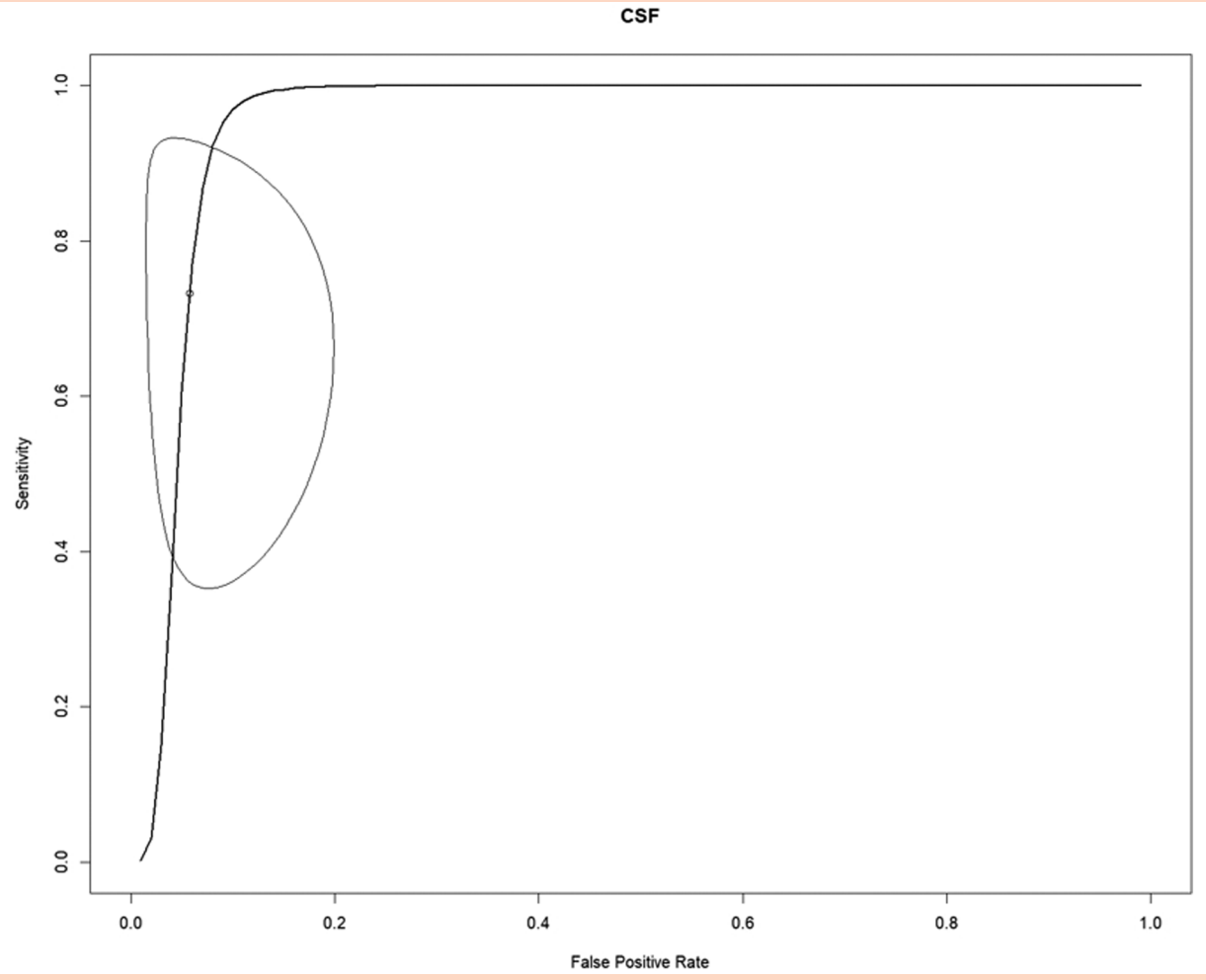


Figure 2. Overall receiver operating characteristic curve for ctDNA in cerebrospinal fluid. Gray lines represent the uncertainty around point estimates (empty circles) for each study.

low-grade tumors ($P = .007$). The pooled sensitivity was 0.57 (95% CI, 0.38-0.75) among 43 low-grade gliomas and 0.84 (95% CI, 0.75-0.90) among 254 high-grade gliomas. When tumors were stratified according to their proximity to CSF spaces, the pooled sensitivity was 0.86 (95% CI, 0.7-0.91) among 146 CSF-adjacent tumors, compared with 0.66 (95% CI, 0.47-0.81) among 62 non-CSF-adjacent tumors. Sensitivity was significantly higher for tumors located adjacent to CSF spaces ($P = .01$). When CSF sensitivity was stratified by disease status, the pooled sensitivity was 0.78 (95% CI, 0.70-0.85) among 146 primary tumors and 0.86 (95% CI, 0.68-0.95) among 57 recurrent tumors. This difference was not statistically significant ($P = .30$).

IDH1 and H3F3A Mutation Detection in CSF

Among 64 patients with IDH1-mutant gliomas, the pooled sensitivity of CSF-based IDH1 mutation detection was 0.68 (95% CI, 0.53-0.80). For the 23 cases with H3F3A mutations the pooled sensitivity was of 0.78 (95% CI, 0.56-0.91).

Discussion

Despite the requirement for histopathological evaluation to establish a definitive CNS tumor diagnosis according to the current WHO classification,[3] there has been a progressive shift toward less invasive approaches in neuro-oncology. ctDNA has emerged as a promising biomarker for liquid biopsy in the detection and management of gliomas. This meta-analysis highlights and supports its clinical utility for detecting tissue-matched mutations. ctDNA detected in CSF demonstrated higher sensitivity (0.79) than plasma ctDNA (0.29); however, both showed high specificity, suggesting that when a tumor-associated mutation is detected, it is unlikely to represent a false-positive finding. The lower sensitivity observed in plasma is likely influenced by the restrictive nature of the blood-brain barrier (BBB). Importantly, no difference was observed between NGS and ddPCR-based studies.

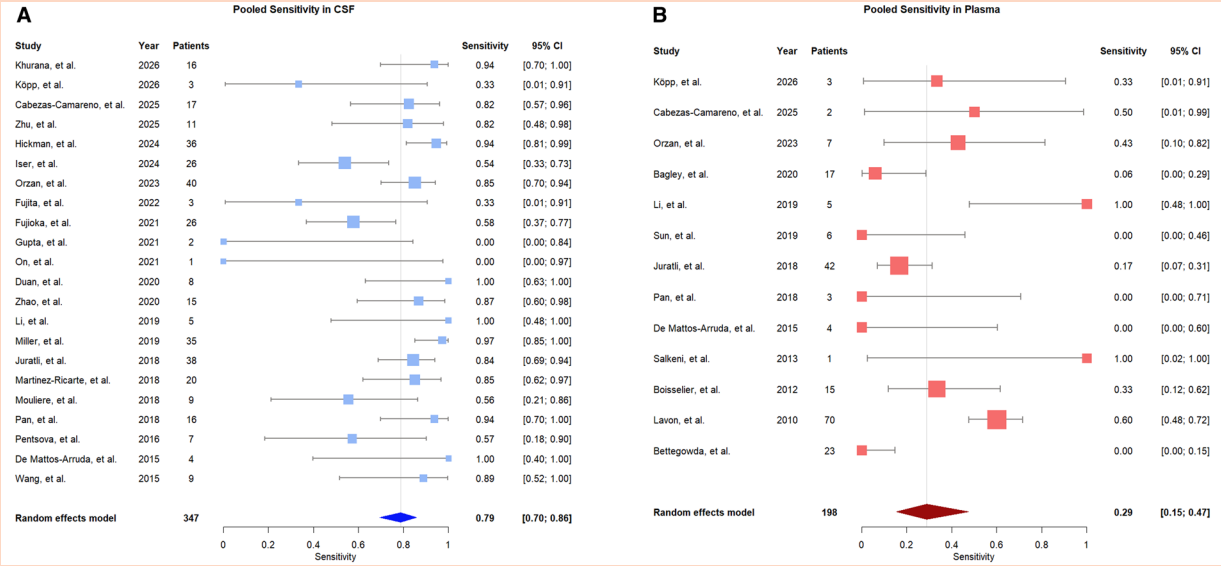


Figure 3. Sensitivities of circulating tumor DNA to identify glioma as reported in CSF (A) and plasma (B) by the indicated article. Square indicates sensitivity reported with corresponding bars indicating 95% CI, the rhombus represents the pooled sensitivity. Abbreviations: CSF, cerebrospinal fluid; TP, true positives.

CSF and Blood ctDNA Comparison

Multiple studies have consistently demonstrated higher sensitivity for CSF ctDNA compared to plasma ctDNA in detecting high-grade gliomas; nevertheless, most of these studies have not reported statistical significance for this difference, likely due to small sample sizes or study design limitations.[16,26,43-48] Our current analysis demonstrates a statistically significant difference in sensitivity between CSF and plasma ctDNA detection of gliomas ($P<.05$), providing statistical evidence for what has been observed as a consistent trend in the literature. Blood-based liquid biopsies are currently used to diagnose and monitor several types of solid tumors; however, clinical implementation in patients with CNS tumors remains limited. It is believed that cfDNA detection in blood is reduced due to the BBB, which limits the tumoral DNA shedding into the bloodstream.[49]Therefore, other biofluids, such as CSF, have been considered as an alternative to detect ctDNA, which has lower levels of cfDNA than blood and increased cell and DNA shedding of CNS malignancies.[50] We confirmed that the detection of ctDNA significantly increased in CSF compared to plasma in gliomas. Both targeted sequencing-based and fragmentomics studies of ctDNA in CSF have shown high specificity with targeted sequencing-based, while plasma ctDNA studies demonstrate lower sensitivity compared to CSF, highlighting the superior performance of CSF-based liquid biopsy approaches over blood-based methods in glioma detection using the commonly available methodologies.[16] CSF-based liquid biopsies could be of particular utility in patients with tumors involving eloquent regions where tissue biopsies carry high risk, even though tissue biopsies remain the gold standard for glioma diagnosis and molecular profiling.[51] Despite CSF retrieval carrying more risks than blood drawing, complications are seldom reported with either procedure, and liquid biopsies afford a broad range of applications with utility not only in primary diagnosis but also in monitoring treatment response and disease progression.[52]

ctDNA as a Liquid Biopsy Compared to Other Methodologies

Among the various liquid biopsy approaches, the analysis of ctDNA has gained prominence due to a favorable balance of advantages over other circulating biomarkers in glioma detection.[52] Each analyte offers a unique window into tumor biology but comes with its own set of challenges. For instance, CTCs provide the distinct advantage of yielding whole, viable cells for comprehensive genomic, transcriptomic, and proteomic analysis.[53] However, their extreme rarity in circulation, especially in CNS tumors, makes their isolation technically demanding and limits their clinical sensitivity.[53]

Another approach involves the analysis of EVs, such as exosomes, which are shed by tumor cells and contain protected molecular cargo like DNA, RNA, and proteins.[54] This encapsulation enhances the stability of the analytes within. Despite this, the clinical utility of EVs is currently hampered by a lack of standardized isolation protocols and the significant challenge of distinguishing tumor-derived EVs from the abundant background of those from healthy cells.[54,55] Similarly, cell-free RNA (cfRNA) is valuable for providing a real-time snapshot of gene expression and detecting key events like gene fusions; however, its practical application is severely limited by the inherent instability of RNA, which is rapidly degraded by ubiquitous enzymes in biofluids.[56] Finally, while protein-based biomarkers can be measured with established, cost-effective assays, they often suffer from poor specificity, as their levels can be elevated in various nonmalignant conditions like inflammation, confounding their interpretation.[57]

It is this powerful combination of high specificity, relative stability, and analytical flexibility that has established ctDNA as the most widely investigated liquid biopsy analyte in oncology and made it the focus of this systematic review and meta-analysis.[52,58] Our findings validate this focus, confirming that ctDNA holds significant promise as a diagnostic tool but also revealing that its efficacy is critically dependent on the biofluid source. This meta-analysis demonstrated the superior performance of ctDNA CSF, which achieved a high diagnostic accuracy with an AUC of 0.95 and a pooled sensitivity of 0.79. In contrast, we identified a key limitation in plasma-based ctDNA, which showed significantly lower sensitivity 0.29, likely due to the BBB. Therefore, while our results favor CSF-derived ctDNA as a powerful complementary tool, they also highlight the clear limitations of blood-based testing and reinforce the need for standardized protocols to optimize its clinical implementation.

Glioma-specific epigenetic alterations represent an additional target for liquid biopsy, as aberrant DNA methylation patterns are well established across CNS tumors.[59] Methylation-based liquid biopsy approaches have shown promising sensitivity and specificity and may provide useful tumor-associated signals even in plasma.[60] In addition to supporting tumor detection and classification, methylation profiling may provide clinically relevant information regarding prognosis and treatment response, including biomarkers such as MGMT promoter methylation.[59] An important advantage of these approaches is that they can interrogate broader epigenetic signatures and do not necessarily require prior knowledge of specific point mutations.[59,60] Therefore, methylation-based liquid biopsy may be considered an alternative approach for the molecular evaluation of CNS tumors.

Sequencing Techniques and ctDNA Fragmentation Patterns

Cell-free deoxyribonucleic acid (cfDNA) is released into biofluids such as blood and CSF by nonmalignant cells when undergoing apoptosis or necrosis.[61] One of the challenges of ctDNA mutation detection is its dilution by cfDNA containing predominantly wild-type DNA, which lacks tumor-specific genetic alterations and can hinder the detection of low-frequency mutations using conventional sequencing methods.[62]

The development of ddPCR and NGS has enabled highly sensitive mutation detection at very low variant allele frequencies (VAFs), helping overcome the challenge of ctDNA dilution by wild-type cfDNA. Reported detection limits can reach approximately 0.001% VAF for ddPCR, whereas conventional NGS generally requires higher VAFs, often around 1%-3%, for reliable detection.[63] In this study, we did not identify any significant difference in sensitivity between the 2 methodologies. However, each offers distinct advantages: ddPCR provides highly sensitive detection of predefined target mutations, whereas NGS enables the simultaneous detection of multiple genetic alterations without requiring prior knowledge of the specific variant.[64] The ctDNA sequencing approach should be selected based on the characteristics of each methodology and the aim of the analysis, as some tumors can be diagnosed based on specific genetic alterations, such as H3 K27 alterations in diffuse midline glioma (DMG), whereas others can be diagnosed based on different genetic alterations, such as telomerase reverse transcriptase (TERT) promoter mutations or epidermal growth factor receptor (EGFR) amplification in glioblastoma.[65,66]

The cfDNA of nonmalignant cells tends to be longer than ctDNA, with nonmalignant cfDNA having an approximate fragment size of 167 bp, while ctDNA tends to be shorter, with a mean length of 145 bp.[67] This characteristic fragment length difference allows for differentiation of cfDNA from ctDNA and enables selective sequencing of shorter fragments to identify tumor-specific mutations and therefore malignancy, improving the results of liquid-biopsy.[54]

Time of Sample Collection and Tumor Characteristics

The timing of sample collection for performing a liquid biopsy is crucial, as the amount of glioma-derived ctDNA in biofluids decreases after treatment. The evidence suggests that the quantity of ctDNA in blood and plasma appears to correlate positively with disease burden, enabling its use not only for primary diagnosis but also for tumor monitoring, particularly when imaging fails to provide an accurate assessment.[16,44] Therefore, standardizing the timing of sample collection in studies is essential to ensure consistent and accurate protocols, especially to distinguish between initial diagnosis and tumor recurrence. However, many studies fail to standardize both the site and time of sample acquisition, introducing bias into their results.

The tumor's location and the site of sample collection are critical factors, particularly in CSF-based analysis. One of the main advantages of liquid biopsies for glioma diagnosis is the potential to avoid brain biopsy. Nevertheless, some studies overlook real-world clinical scenarios by collecting CSF directly from the subarachnoid space or intraventricular system during surgery, which could limit the application of results to real-life clinical scenarios. A more appropriate strategy for clinical practice would be to perform a LP to collect CSF before any surgical intervention. However, this is somewhat challenging under current routine clinical practice, given that LP prior to surgical intervention, while performed in some scenarios (eg suspected lymphoma, medulloblastoma, suspected leptomeningeal disease), are not widely used in all CNS malignancies. Despite the varying sensitivity rates and ctDNA quantities between samples obtained via LP and intracranial reported in previous studies, we did not find a statistical difference between intracranial and LP samples.[7]

Tumor location significantly impacts ctDNA release into biofluids, primarily due to anatomical and physiological barriers. Tumors situated closer to the ventricular system or infiltrating the meninges might exhibit higher ctDNA levels in CSF compared to those located deep within the brain parenchyma.[58] This was confirmed by our results, in which CSF-adjacent tumors demonstrated higher detection rates with CSF-based liquid biopsy. This spatial variability necessitates tailored sampling strategies to optimize ctDNA capture based on tumor location. Furthermore, it also suggests that tumor DNA is shed from the tumor directly into the CSF, rather than reaching it indirectly through the plasma.[31] The BBB selective permeability restricts the passage of large molecules

(including ctDNA) under normal physiological conditions.[58] As such, it plays a pivotal role in modulating ctDNA movement between the CSF and blood. Tumor-induced disruption of the BBB can facilitate ctDNA release into the bloodstream, potentially enhancing detection sensitivity.[16] The extent to which ctDNA can freely traverse from the CSF to the blood remains an area of active investigation, with implications for optimizing sampling sites and improving detection accuracy.

IDH1 and H3F3A Mutations

The identification of specific glioma mutations is of high importance for the prognosis, diagnosis, and treatment of these tumors. One of the benefits of ctDNA-based liquid biopsy is the evaluation of targeted mutations to gain insights into tumor.[68,69] IDH mutations are among the most important genetic alterations in gliomas. Mutations in the IDH1 and IDH2 genes are associated with a more favorable prognosis and may also serve as targets for molecularly targeted therapies.[70] The pooled sensitivity for IDH1, the most frequently mutated IDH gene in gliomas, was 0.68, demonstrating the potential clinical application of liquid biopsy for decision-making in tumor management.

DMGs are tumors located in eloquent regions, where tissue biopsy represents a challenge because of their anatomic location.[71] These tumors are characterized by mutations in histone 3 (H3)-encoding genes. In this meta-analysis, the pooled sensitivity for H3F3A alterations, involving the most commonly altered H3-encoding gene, was 0.78.[72] This highlights the diagnostic utility of ctDNA-based liquid biopsy for the diagnosis of specific glioma entities.

Limitations

While this study provides a comprehensive summary of ctDNA detection in CSF and blood for intracranial gliomas in adult patients, several limitations should be acknowledged. First, this study focused on the detection of tumor-associated molecular alterations in ctDNA rather than on clinical outcomes. Future studies should investigate whether ctDNA detection has prognostic value or influences clinical decision-making and patient outcomes. Second, substantial clinical and methodological heterogeneity was present across the included studies. In particular, limited stratification according to specific WHO CNS5 tumor entities restricted our ability to assess whether ctDNA detection varies across molecularly defined glioma subtypes. Differences in publication year may also have introduced heterogeneity, as sequencing platforms, assay sensitivity, gene-panel coverage, and other technological approaches have evolved considerably over time. In addition, treatment status was inconsistently reported across studies, limiting our ability to distinguish between treatment-naïve patients, patients receiving active treatment, and those with recurrent or progressive disease. These differences may influence ctDNA shedding and detection rates and therefore affect the pooled estimates. The overall risk of bias was rated as moderate, reflecting the heterogeneity among the included studies. Finally, standardized protocols for sample collection, timing, processing, and ctDNA analysis in both CSF and blood are warranted to improve comparability across studies and facilitate clinical implementation.

Conclusion

ctDNA analysis demonstrates promising but variable diagnostic performance in patients with gliomas. CSF ctDNA exhibited superior sensitivity compared to plasma ctDNA. This meta-analysis supports the utility of ctDNA, particularly CSF ctDNA, as a complementary diagnostic and monitoring tool in neuro-oncology. Further trials are needed to establish optimal testing protocols and definitively determine sensitivity and specificity for routine clinical implementation in glioma diagnosis.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

ctDNA | CSF | gliomas | liquid biopsy | meta-analysis

Lay Summary

Gliomas are central nervous system tumors that require tissue testing for diagnosis. Liquid biopsy offers a less invasive way to detect tumor-related genetic alterations by analyzing cerebrospinal fluid (CSF) or blood. We reviewed published studies evaluating the detection of DNA originating from gliomas in blood and CSF. Detection in CSF showed strong overall performance, with an area under the curve of 0.95 and a sensitivity of 0.79, compared with 0.29 in plasma. These findings suggest that CSF circulating tumor DNA may become a useful complementary tool for the characterization of intracranial gliomas in adults.

Author Contributions

Study design: Christian Amezquita-Contreras, Antonio Dono, Yoshua Esquenazi, Leomar Y. Ballester. Data collection: Christian Amezquita-Contreras, Helen Ruvalcaba-Guerrero, Angel Bueno-Alvarez Diego Arellano, William E. Johnson, Antonio Dono. Data analysis: Christian Amezquita-Contreras. Manuscript draft writing: Christian Amezquita-Contreras, Helen Ruvalcaba-Guerrero, Diego Arellano, Antonio Dono. Manuscript editing: Christian Amezquita-Contreras, Helen Ruvalcaba-Guerrero, Diego Arellano, Antonio Dono. Manuscript approval: all authors.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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The data generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Previous Presentations

None.

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