

Review Article

Emerging Biomarkers for Brain Tumors: Advances in Early Detection and Therapeutic Monitoring

Nivetha Mahesh¹, Revanth R²

From, ¹Department of Pharmacy Practice, JKKN College of Pharmacy, Namakkal, Tamil Nadu, India. ²Assistant Professor, Department of Pharmacy Practice, JKKN College of Pharmacy, Namakkal, Tamil Nadu, India.

ABSTRACT

Brain tumors, including primary and metastatic brain tumors, remain a major clinical challenge because of their biological heterogeneity, aggressive behavior, and limited treatment options. Early diagnosis, accurate prognostication, and continuous monitoring are essential for improving patient outcomes. Recent advances in molecular biology and liquid biopsy technologies have identified several promising biomarkers with potential clinical applications. This review summarizes emerging genetic, epigenetic, metabolic, and circulating biomarkers for brain tumors, with particular emphasis on extracellular vesicles (EVs) and cerebrospinal fluid (CSF). Established molecular markers, including isocitrate dehydrogenase (IDH) mutations, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, H3K27M, epidermal growth factor receptor (EGFR) amplification, TP53 and BRAF mutations, and TERT promoter mutations, provide valuable information for tumor classification, prognosis, and therapeutic decision-making. Additional biomarkers such as S100B, YKL-40, microRNAs, choline, and lactate may contribute to disease monitoring and assessment of tumor activity. Advances in next-generation sequencing and liquid biopsy have further enhanced the ability to detect tumor-specific molecular alterations and monitor tumor evolution. EVs are particularly promising because they transport proteins, lipids, DNA, and RNA and may facilitate both biomarker detection and targeted drug delivery across the blood-brain barrier. CSF represents another valuable biomarker source because of its close proximity to brain tumors and higher concentration of tumor-derived molecules compared with peripheral blood. Despite these advances, challenges related to assay standardization, sensitivity, specificity, sampling, and clinical validation remain. Integrating molecular biomarkers, EVs, CSF analysis, and advanced genomic technologies may ultimately enable more accurate diagnosis, personalized treatment, and real-time monitoring of brain tumors.

Key words: Brain tumors, Biomarkers, IDH mutation, MGMT methylation, extracellular vesicles, cerebrospinal fluid, liquid biops

Brain tumors pose a significant clinical challenge because of their complex biology, varied histology, and the need for timely diagnosis and effective treatment [1,2]. They comprise primary brain tumors, which originate within brain tissue, and metastatic brain tumors (BrM), which arise from malignancies elsewhere in the body [3]. Lung, breast, melanoma, colon, kidney, and ovarian cancers are the most common sources of BrM, and approximately 15% of cases have an unknown primary origin [3]. Prognosis in BrM remains poor and varies with the primary cancer type and the extent of metastatic disease [4], median survival after BrM diagnosis is approximately 15 months in lung cancer but only 7 to 10 months in melanoma.

Despite advances in neuroimaging, neurosurgery, stereotactic radiosurgery, and systemic therapies, outcomes have not improved substantially over recent decades, underscoring the need for innovative diagnostic and therapeutic strategies. Advances in molecular biology and genomics have enabled the identification of biomarkers, derived from tumor tissue, blood, or cerebrospinal fluid (CSF), that offer insight into tumor biology, treatment response, and disease progression [5]. Extracellular vesicles (EVs) and circulating tumor DNA (ctDNA) are particularly promising because they reflect the tumor's molecular profile and permit non-invasive monitoring [5,6]. EVs, which include exosomes and microvesicles, mediate intercellular communication and are implicated in tumor progression and metastasis [7,8].

Access this article online

Received – 05th October 2026

Initial Review – 05th October 2026

Accepted – 07th October 2026

Corresponding author: Dr. Revanth R Assistant Professor, Department of Pharmacy Practice, JKKN college of pharmacy, Namakkal, Tamil Nadu.

E-mail: revram95@gmail.com

CSF is increasingly recognized as a valuable biomarker source: it may contain higher concentrations of specific biomarkers than peripheral blood, reflecting the tumor's molecular landscape more accurately [12,13], and CSF ctDNA analysis has revealed somatic alterations consistent with the primary tumor type [14,15]. However, the invasiveness of CSF sampling limits routine clinical application, and its feasibility in broader patient populations requires further study. This review summarizes emerging biomarkers for brain tumors, focusing on the roles of EVs and CSF in early detection and therapeutic monitoring, and aims to elucidate their clinical utility in improving outcomes and guiding personalized treatment.

2. EMERGING BIOMARKERS FOR BRAIN TUMORS

2.1 IDH Mutation

Mutations in the isocitrate dehydrogenase genes IDH1 and IDH2 are critical biomarkers in gliomas [16]. They confer a gain of function that produces 2-hydroxyglutarate (2-HG), an oncometabolite that promotes tumorigenesis by altering cellular metabolism and epigenetic regulation [17]. IDH-mutant gliomas show a lower grade at diagnosis, slower growth, and improved overall survival compared with IDH wild-type tumors [18]. IDH mutations are also linked to the glioma CpG island methylation phenotype (G-CIMP), characterized by widespread DNA methylation changes [19], which is thought to influence tumor biology and response to therapy, particularly temozolomide, making IDH status vital for treatment planning and prognostication [20]. In current clinical practice, IDH mutation status is an essential component of the integrated molecular classification of diffuse gliomas. It contributes to tumor diagnosis and grading when interpreted alongside histological findings and other molecular alterations. IDH status also provides important prognostic information and may influence treatment planning. Furthermore, the availability of IDH-targeted therapies has increased the clinical relevance of identifying IDH mutations in selected patients. However, IDH status should be interpreted together with other clinical and molecular features rather than used as an isolated predictor of outcome [19,20].

2.2 MGMT Promoter Methylation

O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is a significant biomarker in glioblastoma, influencing treatment response and prognosis [21]. MGMT is a DNA repair enzyme that counteracts alkylating agents such as temozolomide (TMZ); promoter methylation silences the gene, decreasing MGMT expression and enhancing TMZ sensitivity [22]. Patients with MGMT methylation show improved overall and progression-free survival with TMZ [23–25]. This value is particularly pronounced in the context of IDH mutations, where combined assessment of both biomarkers stratifies patients into

distinct risk categories and aids tailored management [23]. MGMT promoter methylation has particular clinical relevance in glioblastoma because it is associated with a greater likelihood of benefit from temozolomide-based chemotherapy. In clinical practice, MGMT methylation status helps clinicians interpret the expected benefit of alkylating-agent treatment, particularly when considering treatment options for older or medically vulnerable patients. Nevertheless, its interpretation depends on the clinical context, assay methodology, and other patient and tumor characteristics. MGMT promoter methylation is therefore best considered a treatment-response biomarker rather than a standalone diagnostic marker [24,25]

2.3 H3K27M Mutation

The H3K27M mutation, in the histone H3 gene (H3F3A), is mainly associated with diffuse intrinsic pontine gliomas (DIPGs) and other high-grade gliomas [26,27]. By altering histone H3 methylation, it causes widespread epigenetic changes that promote tumor growth and survival [28]. It indicates poor prognosis, occurring in aggressive tumors resistant to conventional therapies [29], and is used in molecular diagnostics to classify tumors and guide treatment. Targeting the epigenetic changes it induces, including with small-molecule inhibitors of the affected pathways, may offer new therapeutic avenues [30].

2.4 EGFR Amplification

Epidermal growth factor receptor (EGFR) amplification occurs in approximately 40% of glioblastomas [31]. It causes EGFR overexpression, promoting tumor cell proliferation, survival, and invasion, and is associated with a more aggressive phenotype and poorer prognosis [32]. EGFR alterations can guide targeted therapy, such as tyrosine kinase inhibitors, although these have shown limited efficacy in glioblastoma; novel agents targeting EGFR and its downstream pathways are under development [33].

2.5 TP53 Mutations

TP53 mutations are prevalent in brain tumors, particularly glioblastomas. TP53 encodes p53, a tumor suppressor that regulates the cell cycle, DNA repair, and apoptosis [34]. Mutations often cause loss of function, allowing unchecked proliferation and survival [35], and are associated with more aggressive behavior and poorer outcomes. They frequently co-occur with other alterations, such as IDH mutations and MGMT methylation, informing tumor biology and therapeutic vulnerabilities, and assessing TP53 status is essential for prognosis and treatment guidance in glioma [36].

2.6 BRAF Mutations

BRAF mutations, particularly V600E, occur in a subset of gliomas, including pilocytic astrocytomas and some high-grade gliomas [37]. BRAF is a key component of the MAPK

signaling pathway, and its mutation causes constitutive activation that promotes cell proliferation and survival [38]. BRAF mutations are associated with specific clinical features and can influence treatment decisions [39]. BRAF inhibitors have shown promise in preclinical models and early trials, but resistance is a concern, and combination strategies require further research [39].

2.7 Megalin

Megalin, a member of the low-density lipoprotein receptor family, mediates the uptake of ligands, including hormones and nutrients, in the brain. Its expression is linked to glioma pathophysiology, may influence tumor growth and therapeutic response, and elevated levels are associated with poor prognosis [40]. Its mechanistic role and potential as a therapeutic target or treatment-response biomarker remain under investigation.

2.8 S100B

S100B is a calcium-binding protein predominantly expressed in astrocytes, and its CSF and serum levels have been investigated as biomarkers for brain tumors [41]. Elevated S100B is associated with poor prognosis and tumor progression in gliomas and is thought to influence tumor cell proliferation, migration, and survival [42]. It is also being studied for monitoring treatment response and recurrence [41]. Its non-invasive nature makes it attractive, although validation in larger cohorts is needed [43]. Despite its potential value, S100B has limited diagnostic specificity for brain tumors because its concentration may also increase in other neurological conditions, including traumatic brain injury and stroke. Its levels may be influenced by non-tumor-related tissue damage and other clinical factors. Therefore, S100B should not be used as a standalone diagnostic marker for brain tumors. Its potential utility is better assessed in conjunction with clinical findings, neuroimaging, and more tumor-specific molecular biomarkers. Further validation in well-characterized patient cohorts is required to establish its diagnostic performance and clinical value for disease monitoring.

2.9 CSF Biomarkers (YKL-40)

YKL-40, a glycoprotein secreted by activated astrocytes and microglia, has emerged as a promising biomarker in brain tumors [44]. Elevated YKL-40 in CSF and serum correlates with tumor presence, progression, and poor prognosis in gliomas [45], and it is believed to participate in inflammatory processes and tissue remodeling within the tumor microenvironment [44]. Its measurement may provide information on tumor activity and treatment response [46], and its role in glioma biology and potential as a therapeutic target or prognostic marker are under study.

2.10 ctDNA

ctDNA is a novel biomarker for monitoring tumor dynamics in gliomas. Shed from tumor cells into the bloodstream, it can be detected by advanced sequencing [47] and identifies specific tumor mutations, providing insight into tumor heterogeneity and evolution. It has potential as a non-invasive biomarker for early detection of recurrence, assessment of treatment response, and monitoring of minimal residual disease; its clinical application remains under investigation, but it holds great promise for glioma management [48,49]. Despite its potential, the clinical application of circulating tumor DNA (ctDNA) in brain tumors faces several limitations. Tumor-derived ctDNA may be present at very low concentrations in peripheral blood because the blood–brain barrier restricts the release of tumor-associated material into the systemic circulation. Consequently, the sensitivity of blood-based ctDNA assays may be limited, particularly in patients with small tumors or low tumor burden. A negative blood-based result does not necessarily exclude the presence of a brain tumor or a clinically relevant molecular alteration. In addition, assay sensitivity, pre-analytical sample handling, and tumor heterogeneity can influence detection. Cerebrospinal fluid (CSF) may provide a higher yield of tumor-derived DNA in selected patients, although its collection is invasive and may not be suitable for every patient.

2.11 TERT Promoter Mutation

TERT promoter mutations are common in gliomas and are associated with telomerase activation, enhanced cellular immortality, and tumorigenesis [50,51]. Particularly prevalent in high-grade gliomas and linked to poor prognosis, they help differentiate tumor types and predict clinical outcomes [52], and are often assessed alongside other genetic alterations to build a comprehensive molecular profile. Their functional implications and potential as therapeutic targets are under investigation [53].

2.12 Choline and Lactate

Choline and lactate are metabolites measurable by magnetic resonance spectroscopy (MRS) and are associated with tumor metabolism in gliomas. Elevated choline indicates increased cellular membrane turnover, a hallmark of tumor proliferation, whereas elevated lactate reflects anaerobic metabolism, often seen in hypoxic tumor environments. Their assessment provides insight into tumor aggressiveness, treatment response, and recurrence, and MRS, as a non-invasive technique, allows real-time monitoring of tumor metabolism in clinical glioma management. [52]

2.13 miRNA

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression and are implicated in glioma pathogenesis. Specific miRNA profiles are associated with

glioma subtypes and provide insight into tumor behavior, prognosis, and treatment response [54]. Their dysregulation affects pathways governing proliferation, apoptosis, and invasion, and their use as diagnostic and prognostic biomarkers and in targeted therapies is under investigation; their non-invasive detection in body fluids further enhances their appeal [55].

3. ADVANCES IN BIOMARKER DISCOVERY

Advanced molecular profiling and liquid biopsy technologies have greatly enhanced biomarker discovery and validation, enabling more precise detection and monitoring of brain tumors and better clinical outcomes.

3.1 Molecular Profiling Techniques

Next-generation sequencing and biomarker identification

Next-generation sequencing (NGS) has revolutionized molecular profiling by enabling comprehensive analysis of genetic alterations at an unprecedented scale. In brain tumors, it provides deep insight into the genomic landscape and enables the identification of novel biomarkers [56], including mutations in IDH1, the TERT promoter, and BRAF that are key glioma biomarkers for diagnosis, prognosis, and therapeutic decision-making [57]. Whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted sequencing detect mutations, copy number variations, and gene fusions often missed by traditional methods [58]. Simultaneous high-resolution analysis of multiple genes and integration with other omics data (e.g., transcriptomics, proteomics) further enhance biomarker identification.

Traditional methods versus modern genomic approaches

Traditional methods, such as immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH), are widely used to detect specific proteins and genetic alterations but are limited by low throughput, inability to detect complex genomic alterations, and reliance on prior knowledge of the target. NGS offers comprehensive analysis of thousands of genes simultaneously, enabling discovery of novel biomarkers undetectable by traditional methods; high sensitivity for low-frequency mutations and subclonal populations, giving a more accurate representation of tumor heterogeneity; and speed and efficiency, as modern platforms generate vast data quickly enough for clinical application. [57]

3.2 Liquid Biopsy Innovations

Liquid biopsy is an emerging, non-invasive technique that detects and monitors biomarkers in biofluids such as blood, CSF, and urine, and is particularly advantageous in brain tumors, for which traditional biopsy is invasive and risky [59]. Key biomarker sources include ctDNA, which carries tumor-specific genetic alterations detectable in the bloodstream and

has shown promise in detecting brain tumors and monitoring treatment response [60]; circulating tumor cells (CTCs), shed into the bloodstream, which provide information on tumor characteristics and metastatic potential [61] and EVs, including exosomes, which contain tumor-derived proteins, RNA, and DNA [7].

4. ROLE OF EXTRACELLULAR VESICLES IN INTERCELLULAR COMMUNICATION AND TUMOR BIOLOGY

EVs, which comprise membrane-bound vesicles such as exosomes and microvesicles, are released by all cell types and found in body fluids including blood, urine, saliva, and CSF. By transporting proteins, lipids, RNA, DNA, and metabolites, they are essential mediators of intercellular communication in physiological and pathological processes.

4.1 EVs in Communication Between Tumor Cells and the Tumor Microenvironment

The tumor microenvironment is a complex, dynamic system of interactions among tumor cells, stromal cells, immune cells, and the extracellular matrix. EVs are critical components of this network, transferring molecular signals that significantly influence tumor behavior.

Tumor progression and metastasis: Tumor-derived EVs promote tumor progression and metastasis [62]. They carry oncogenic proteins and nucleic acids that are taken up by surrounding cells, altering gene expression and promoting a more malignant phenotype; for example, EVs can transfer mutated oncogenes such as Ras or p53, potentially transforming normal cells into cancerous ones. They also carry growth factors, cytokines, and angiogenic factors that stimulate tumor cell proliferation and angiogenesis, which is critical for tumor growth and metastasis [63,64].

Immune modulation and evasion: Tumor-derived EVs can carry immunomodulatory molecules such as PD-L1, which inhibit cytotoxic T cells and allow tumor cells to evade immune surveillance. They can also alter immune cell function in the tumor microenvironment, for example by converting macrophages to a tumor-promoting (M2) phenotype or inducing regulatory T cells (Tregs) that suppress the antitumor immune response [65].

Pre-metastatic niches: Before metastasizing, tumor cells often prepare distant sites by secreting EVs that recruit bone marrow-derived cells, increase vascular permeability, and modulate the extracellular matrix, creating a niche that supports the survival and growth of metastatic tumor cells [66].

4.2 Mechanisms of EV Release and Uptake

Exosome biogenesis. Exosomes form within the endosomal system. The cell membrane invaginates to form an early

endosome, which matures by inward budding into multivesicular bodies (MVBs) containing intraluminal vesicles (ILVs) [64]. These ILVs, 30 to 100 nm in diameter, are the precursors of exosomes. MVBs either fuse with lysosomes, degrading their contents, or fuse with the plasma membrane, releasing the ILVs extracellularly as exosomes [64,67].

Microvesicle formation. Microvesicles form by outward budding of the plasma membrane, involving cytoskeletal rearrangement and lipid redistribution that cause the membrane to bulge and pinch off. They are generally larger than exosomes, ranging from 100 nm to 1 μ m [68,69].

Uptake by recipient cells. EVs interact with recipient cells through several mechanisms. In direct membrane fusion, EVs deliver cargo directly into the cytoplasm, a route particularly efficient for membrane proteins and lipids [70]. In receptor-mediated endocytosis, recipient cell receptors recognize EV surface ligands, and the internalized EV releases its cargo from an endosome into the cytoplasm [71]. Larger EVs, such as microvesicles, can be engulfed by phagocytosis or macropinocytosis, more commonly in phagocytic cells such as macrophages [71]. EVs may also act without internalization by engaging cell surface receptors and initiating signaling cascades; for example, EVs carrying Wnt proteins can activate Wnt signaling, influencing proliferation and differentiation [70].

4.3 Overall Impact of EV-Mediated Communication in Tumor Biology

EV-mediated communication between tumor cells and their microenvironment is a major factor in cancer progression [72]. By transferring oncogenic molecules, modulating immune responses, and preparing distant sites for metastasis, EVs enable tumors to grow more aggressively and evade therapy; understanding EV release, uptake, and function is therefore crucial for developing strategies that disrupt this communication [72,73].

4.4 Mechanism of EVs in Crossing the Blood-Brain Barrier

Because EVs carry and deliver proteins, lipids, and nucleic acids, they are versatile drug delivery tools [74]. Significantly, EVs can cross the BBB, which is typically impermeable to most substances, owing primarily to their small size, biocompatibility, and surface proteins that facilitate uptake by brain endothelial cells. Their natural origin also allows them to evade the immune system, reducing rapid clearance and enhancing their potential as drug carriers [75,76].

4.5 Applications of EVs in Targeted Drug Delivery

By traversing the BBB, EVs enable targeted drug delivery in central nervous system (CNS) disorders and brain tumors. Encapsulating small molecules, proteins, or RNA within EVs can achieve targeted brain delivery, increasing efficacy while

minimizing systemic side effects, which is particularly advantageous for chemotherapy, where traditional treatments often fail because of the restrictive BBB [77].

4.6 Therapeutic Implications in Brain Tumor Treatment

Glioblastomas and other brain tumors are difficult to treat because of the BBB and their infiltrative nature. EVs can be engineered to carry anticancer drugs, RNA interference molecules, or gene-editing tools directly to tumor cells, and EVs derived from specific cell types, such as stem cells with inherent tumor-targeting properties, may further increase precision and effectiveness [78,79]. Recent preclinical studies show that EVs loaded with chemotherapeutic agents such as doxorubicin or paclitaxel reduced tumor size and improved survival in animal models, and displaying tumor-specific ligands on the EV surface may further enhance targeting and efficacy [80]. Extracellular vesicles have potential applications both as diagnostic biomarkers and as therapeutic delivery systems. However, the clinical evidence must be interpreted according to the disease context and intended application. Clinical trials involving EVs in brain tumors are particularly relevant to this review because they may provide direct evidence regarding safety, feasibility, biomarker performance, or therapeutic potential in the central nervous system. Trials conducted in other diseases are included only to illustrate broader developments in EV-based clinical translation and should not be interpreted as evidence of efficacy in brain tumors. Disease-specific validation and well-designed clinical studies remain necessary before EV-based approaches can be adopted in routine brain tumor management. Clinical trials involving EVs are summarized in Table 1.

5.1 Overview of CSF Analysis for Brain Tumor Detection

Brain tumors are difficult to diagnose and manage given the brain's complexity and inaccessibility, and tissue biopsy, although effective, carries significant risks and is often unsuitable. CSF has therefore emerged as a promising, less invasive, and potentially more accurate diagnostic alternative, particularly where conventional methods prove inadequate [12,13]. CSF, a clear fluid that cushions the brain and spinal cord, is in direct contact with the CNS and is ideally positioned to capture tumor-related biomarkers released from brain tumor cells, including ctDNA, miRNAs, proteins, and EVs [88].

5.2 Importance in Challenging Diagnostic Cases

Diagnosis is particularly difficult when tumors are small, deeply situated, or associated with non-specific symptoms [89]. Imaging alone may not be definitive, and biopsy risks include hemorrhage, neurological damage, and infection. CSF analysis offers a safer, more accessible way to obtain diagnostic information, including when other methods fail to yield clear results [12]. Lumbar puncture is relatively simple and minimally invasive and permits repeated sampling, facilitating

dynamic monitoring of tumor progression, treatment response, and early recurrence [90].

5.3 Abundance of Biomarkers in CSF Compared with Peripheral Fluids

CSF is superior to peripheral fluids such as blood for detecting brain tumor biomarkers. The BBB, although essential for protecting the brain, limits the presence of tumor biomarkers in the bloodstream, making peripheral blood less reliable for detecting brain-specific abnormalities [91]. CSF is not similarly restricted, and tumor-associated biomarkers are consequently more abundant in CSF than in blood. For instance, ctDNA is found at higher concentrations in CSF than in plasma [92], which is particularly important for identifying mutations linked to brain tumors, such as those in IDH1, TP53, and EGFR, that are crucial for diagnosis and personalized treatment [93].

5.4 Clinical Studies and Comparative Data

In a study detecting tumor-specific mutations in brain tumor patients, CSF ctDNA had a detection sensitivity of 100%, compared with only 37.5% for plasma ctDNA, underscoring the limitations of peripheral blood and positioning CSF as a more reliable source [12]. CSF is also superior for detecting circulating nucleic acids, such as miRNAs and other small non-coding RNAs, which are more concentrated and stable in CSF than in blood, where they may be degraded by enzymes or

diluted by larger plasma volumes [94]. Proteins and EVs are likewise more concentrated in CSF and help characterize tumor behavior and identify therapeutic targets; for instance, glial fibrillary acidic protein (GFAP) and extracellular matrix components such as tenascin and osteopontin are often elevated in the CSF of patients with gliomas, providing valuable diagnostic and prognostic information [95].

5.5 Implications for Brain Tumor Management

The greater abundance of biomarkers in CSF improves diagnostic accuracy and disease management. By giving a clearer view of the tumor's genetic and molecular landscape, CSF biomarkers enable personalized treatment, including selection of targeted therapies based on mutations detected in CSF, monitoring of treatment efficacy, and detection of early recurrence [96]. They may also reduce the need for repeated invasive procedures such as brain biopsy by allowing ongoing monitoring, which is particularly important for patients with high-risk tumors or those who are not surgical candidates because of their overall health [12]. CSF is thus a powerful biomarker source for brain tumor detection and management, particularly in challenging diagnostic cases; its ability to reveal the tumor's genetic and molecular characteristics, together with its accessibility and minimal invasiveness, makes CSF analysis an invaluable tool in brain cancer care [97].

Table 1: Clinical trials involving "Extracellular Vesicles" (EVs) as biomarkers or therapeutic tools

Trial registration number	Disease / clinical indication	Study phase	Biomarker or therapeutic application	EV Source / Type	Key Findings / Outcomes	Status
NCT03384433 [81]	Glioblastoma	Phase I	Evaluate safety and efficacy of EVs loaded with siRNA	Mesenchymal Stem Cell-Derived EVs	Safe and tolerable with potential therapeutic effects	Completed
NCT02657460 [82]	Non-Small Cell Lung Cancer (NSCLC)	Phase II	Biomarker for early detection	Tumor-Derived EVs	Showed potential as a non-invasive diagnostic marker	Completed
NCT04394572 [83]	COVID-19	Phase I/II	Evaluate the efficacy of EVs in reducing inflammation	Plasma-Derived EVs	Reduced inflammation and improved clinical outcomes	Ongoing
NCT02862315 [84]	Alzheimer's Disease	Phase I	Assess EVs as a therapeutic tool	Neuronal-Derived EVs	Indicated potential in delivering therapeutic agents	Completed
NCT03468426 [85]	Pancreatic Cancer	Phase II	Biomarker for monitoring treatment response	Tumor-Derived EVs	Correlated EVs with treatment response	Completed
NCT03608631 [86]	Traumatic Brain Injury	Phase I	Explore EVs as a diagnostic biomarker	Neural Stem Cell-Derived EVs	EVs reflected injury severity and prognosis	Ongoing
NCT04327470 [87]	Multiple Myeloma	Phase II	Biomarker for disease progression	B-cell-Derived EVs	Correlated EV levels with disease progression	Ongoing

CONCLUSION

Molecular biomarkers are increasingly important in the classification, prognostic assessment, and therapeutic management of brain tumors. Among established biomarkers, IDH mutation status contributes to the integrated diagnosis and prognostic assessment of diffuse gliomas, whereas MGMT promoter methylation helps predict the likelihood of benefit from temozolomide-based treatment in glioblastoma. H3 K27 alterations, EGFR amplification, and other molecular changes provide additional diagnostic or prognostic information when interpreted within the appropriate clinical and pathological context. Emerging biomarkers, including circulating tumor DNA, microRNAs, extracellular vesicles, and cerebrospinal fluid-derived molecular markers, offer opportunities for minimally invasive tumor characterization and longitudinal monitoring. CSF-based assays may be particularly informative in selected patients, while blood-based assays offer easier repeat sampling but may be limited by the low abundance of tumor-derived material. EV-associated molecules and specific miRNA profiles are promising research areas, although their clinical utility requires further validation. Major barriers to clinical implementation include the lack of standardized collection and analytical procedures, variable assay sensitivity and specificity, tumor heterogeneity, limited validation in large prospective cohorts, and uncertainties regarding cost-effectiveness and clinical decision thresholds. Invasive sampling requirements, particularly for CSF analysis, also restrict routine use in some patients. Future studies should prioritize harmonized methods, independent clinical validation, and evaluation of whether biomarker-guided decisions improve patient outcomes. Integrating established molecular markers with validated liquid biopsy approaches may support more personalized diagnosis, treatment selection, and monitoring of brain tumors.

REFERENCES

1. Kalita-de Croft P, Joshi V, Saunus JM, Lakhani SR. Emerging Biomarkers for Diagnosis, Prevention and Treatment of Brain Metastases-From Biology to Clinical Utility. *Diseases*. 2022;10(1):11. doi: 10.3390/diseases10010011
2. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013--2017. *Neuro-Oncology*. 2020;22(Supplement_1):iv1-iv96. doi: 10.1093/neuonc/noaa200
3. Suh JH, Kotecha R, Chao ST, Ahluwalia MS, Sahgal A, Chang EL. Current approaches to the management of brain metastases. *Nature Reviews Clinical Oncology*. 2020;17(5):279-299. doi: 10.1038/s41571-019-0320-3
4. SN Kalkanis, D Kondziolka, Gaspar L, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. Nih.gov. Published 2014. Accessed August 24, 2024. <https://www.ncbi.nlm.nih.gov/books/NBK79197/>
5. Duffy MJ. Tumor Markers in Clinical Practice: A Review Focusing on Common Solid Cancers. *Medical Principles and Practice*. 2013;22(1):4-11. doi: 10.1159/000338393
6. Lane RE, Korbie D, Hill MM, Trau M. Extracellular vesicles as circulating cancer biomarkers: opportunities and challenges. *Clinical and Translational Medicine*. 2018;7(1). doi: 10.1186/s40169-018-0192-7
7. Kalluri R, McAndrews KM. The role of extracellular vesicles in cancer. *Cell*. 2023;186(8):1610-1626. doi: 10.1016/j.cell.2023.03.010
8. Kalluri R. The biology and function of exosomes in cancer. *Journal of Clinical Investigation*. 2016;126(4):1208-1215. doi: 10.1172/jci81135
9. Huber HJ, Holvoet P. Exosomes. *Current Opinion in Lipidology*. 2015;26(5):412-419. doi: 10.1097/mol.0000000000000214
10. Tao SC, Guo SC. Role of extracellular vesicles in tumour microenvironment. *Cell Communication and Signaling*. 2020;18(1). doi: 10.1186/s12964-020-00643-5
11. Elsharkasy OM, Nordin JZ, Hagey DW, et al. Extracellular vesicles as drug delivery systems: Why and how? *Advanced Drug Delivery Reviews*. 2020;159:332-343. doi: 10.1016/j.addr.2020.04.004
12. Xiao F, Lv S, Zong Z, et al. Cerebrospinal fluid biomarkers for brain tumor detection: clinical roles and current progress. *American journal of translational research*. 2020;12(4):1379-1396. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7191171/>
13. Halawa TF, Saleh Baeesa, Fadol MM, et al. The Role of Liquid Biopsy in the Diagnosis and Prognosis of WHO Grade 4 Astrocytoma. *Cureus*. 2023;15(6):e41221. doi: 10.7759/cureus.41221
14. Jin P, Munson JM. Fluids and flows in brain cancer and neurological disorders. *WIREs mechanisms of disease*. 2022;15(1):e1582. doi: 10.1002/wsbm.1582
15. Dimosthenis Papadimitrakakis, Miltiadis Perdikakis, Gargalionis AN, Papavassiliou AG. Biomarkers in Cerebrospinal Fluid for the Diagnosis and Monitoring of Gliomas. *Biomolecules*. 2024;14(7):801-801. doi: 10.3390/biom14070801
16. Murugan AK, Alzahrani AS. Isocitrate Dehydrogenase IDH1 and IDH2 Mutations in Human Cancer: Prognostic Implications for Gliomas. *British Journal of Biomedical Science*. 2022;79. doi: 10.3389/bjbs.2021.10208
17. Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature*. 2009;462(7274):739-744. doi: 10.1038/nature08617
18. Thien N. The Distribution and Significance of IDH Mutations in Gliomas. *IntechOpen eBooks*. Published online January 19, 2022. doi: 10.5772/intechopen.97380
19. Han S, Liu Y, Cai SJ, et al. IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. *British Journal of Cancer*. 2020;122(11):1580-1589. doi: 10.1038/s41416-020-0814-x
20. Sharma N, Mallela AN, Shi DD, et al. Isocitrate dehydrogenase mutations in gliomas: A review of current understanding and trials. *Neuro-Oncology Advances*. 2023;5(1). doi: 10.1093/nojnl/vdad053
21. Butler M, Pongor L, Su YT, et al. MGMT Status as a Clinical Biomarker in Glioblastoma. *Trends in Cancer*. 2020;6(5):380-391. doi: 10.1016/j.trecan.2020.02.010

22. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *The New England Journal of Medicine*. 2005;352(10):997-1003. doi: 10.1056/NEJMoa043331
23. Yang P, Zhang W, Wang Y, et al. IDH mutation and MGMT promoter methylation in glioblastoma: results of a prospective registry. *Oncotarget*. 2015;6(38):40896-40906. doi: 10.18632/oncotarget.5683
24. Leske H, Ulrike Camenisch Gross, Hofer S, et al. MGMT methylation pattern of long-term and short-term survivors of glioblastoma reveals CpGs of the enhancer region to be of high prognostic value. *Acta Neuropathologica Communications*. 2023;11(1). doi: 10.1186/s40478-023-01622-w
25. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *The Lancet Oncology*. 2009;10(5):459-466. doi: 10.1016/s1470-2045(09)70025-7
26. Martin, Saratsis AM, Geurts M, Franceschi E. H3 K27M-altered Glioma and Diffuse Intrinsic Pontine Glioma: Semi-systematic Review of Treatment Landscape and Future Directions. *Neuro-oncology*. 2023;26(2):S110-S124. doi: 10.1093/neuonc/noad220
27. Wu G, Broniscer A, McEachron TA, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nature Genetics*. 2012;44(3):251-253. doi: 10.1038/ng.1102
28. Saratsis AM, Knowles T, Petrovic A, Nazarian J. H3K27M Mutant Glioma: Disease Definition and Biological Underpinnings. *Neuro-Oncology*. 2023;26(Supplement_2):S92-S100. doi: 10.1093/neuonc/noad164
29. Mosaab A, El-Ayadi M, Khorshed EN, et al. Histone H3K27M Mutation Overrides Histological Grading in Pediatric Gliomas. *Scientific Reports*. 2020;10(1):8368. doi: 10.1038/s41598-020-65272-x
30. Gojo J, Pavelka Z, Zapletalova D, et al. Personalized Treatment of H3K27M-Mutant Pediatric Diffuse Gliomas Provides Improved Therapeutic Opportunities. *Frontiers in Oncology*. 2020;9:1436. doi: 10.3389/fonc.2019.01436
31. Jörg Felsberg, Hentschel B, Kaulich K, et al. Epidermal Growth Factor Receptor Variant III (EGFRvIII) Positivity in EGFR-Amplified Glioblastomas: Prognostic Role and Comparison between Primary and Recurrent Tumors. *Clinical Cancer Research*. 2017;23(22):6846-6855. doi: 10.1158/1078-0432.CCR-17-0890
32. Hölzl D, Hutarew G, Zellinger B, et al. EGFR Amplification Is a Phenomenon of IDH Wildtype and TERT Mutated High-Grade Glioma: An Integrated Analysis Using Fluorescence In Situ Hybridization and DNA Methylation Profiling. *Biomedicines*. 2022;10(4):794. doi: 10.3390/biomedicines10040794
33. Armocida D, Pesce A, Frati A, Santoro A, Salvati M. EGFR amplification is a real independent prognostic impact factor between young adults and adults over 45yo with wild-type glioblastoma? *Journal of Neuro-Oncology*. 2019;146(2):275-284. doi: 10.1007/s11060-019-03364-z
34. Noor H, Briggs NE, McDonald KL, Holst J, Vittorio O. TP53 Mutation Is a Prognostic Factor in Lower Grade Glioma and May Influence Chemotherapy Efficacy. *Cancers*. 2021;13(21):5362. doi: 10.3390/cancers13215362
35. Rivlin N, Brosh R, Oren M, Rotter V. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. *Genes & Cancer*. 2011;2(4):466-474. doi: 10.1177/1947601911408889
36. Olafson LR, Gunawardena M, Nixdorf S, McDonald KL, Rapkins RW. The role of TP53 gain-of-function mutation in multifocal glioblastoma. *Journal of Neuro-Oncology*. 2020;147(1):37-47. doi: 10.1007/s11060-019-03318-5
37. Schreck KC, Pinky Langat, Bhawe VM, et al. Integrated molecular and clinical analysis of BRAF-mutant glioma in adults. *npj Precision Oncology*. 2023;7(1). doi: 10.1038/s41698-023-00359-y
38. H D, Gr B, C C, et al. Mutations of the BRAF gene in human cancer. *Nature*. Published June 27, 2002. <https://pubmed.ncbi.nlm.nih.gov/12068308/>
39. Vincenzo Di Nunno, Gatto L, Tosoni A, Bartolini S, Franceschi E. Implications of BRAF V600E mutation in gliomas: Molecular considerations, prognostic value and treatment evolution. *Frontiers in Oncology*. 2023;12. doi:https://doi.org/10.3389/fonc.2022.1067252
40. Liang J, Lv X, Lu C, et al. Prognostic factors of patients with Gliomas -- an analysis on 335 patients with Glioblastoma and other forms of Gliomas. *BMC Cancer*. 2020;20(1). doi:https://doi.org/10.1186/s12885-019-6511-6
41. Holla FK, Postma TJ, Blankenstein MA, et al. Prognostic value of the S100B protein in newly diagnosed and recurrent glioma patients: a serial analysis. *Journal of Neuro-Oncology*. 2016;129(3):525-532. doi: 10.1007/s11060-016-2204-z
42. Wang H, Zhang L, Zhang IY, et al. S100B Promotes Glioma Growth through Chemoattraction of Myeloid-Derived Macrophages. *Clinical Cancer Research*. 2013;19(14):3764-3775. doi: 10.1158/1078-0432.ccr-12-3725
43. Wang H, Mao X, Ye L, Cheng H, Dai X. The Role of the S100 Protein Family in Glioma. *Journal of Cancer*. 2022;13(10):3022-3030. doi: 10.7150/jca.73365
44. Llorens F, Thüne K, Tahir W, et al. YKL-40 in the brain and cerebrospinal fluid of neurodegenerative dementias. *Molecular Neurodegeneration*. 2017;12(1). doi: 10.1186/s13024-017-0226-4
45. Iwamoto FM, Hottinger AF, Karimi S, et al. Serum YKL-40 is a marker of prognosis and disease status in high-grade gliomas. *Neuro-oncology*. 2011;13(11):1244-1251. doi: 10.1093/neuonc/nor117
46. Boisen MK, Holst CB, Consalvo N, Chinot OL, Johansen JS. Plasma YKL-40 as a biomarker for bevacizumab efficacy in patients with newly diagnosed glioblastoma in the phase 3 randomized AVAglio trial. *Oncotarget*. 2017;9(6):6752-6762. doi: 10.18632/oncotarget.22886
47. Müller Bark J, Kulasinghe A, Chua B, Day BW, Punyadeera C. Circulating biomarkers in patients with glioblastoma. *British Journal of Cancer*. 2019;122:295-305. doi: 10.1038/s41416-019-0603-6
48. Kang Y, Lin X, Kang D. Diagnostic value of circulating tumor DNA in molecular characterization of glioma. *Medicine*. 2020;99(33):e21196. doi: 10.1097/md.00000000000021196
49. Jones JJ, Nguyen H, Wong SQ, et al. Plasma ctDNA liquid biopsy of IDH1, TERTp, and EGFRvIII mutations in glioma. *Neuro-Oncology Advances*. 2024;6(1). doi: 10.1093/noajnl/vdae027

50. Arita H, Matsushita Y, Machida R, et al. TERT promoter mutation confers favorable prognosis regardless of 1p/19q status in adult diffuse gliomas with IDH1/2 mutations. *Acta Neuropathologica Communications*. 2020;8(1). doi: 10.1186/s40478-020-01078-2
51. Killela PJ, Reitman ZJ, Jiao Y, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. *Proceedings of the National Academy of Sciences*. 2013;110(15):6021-6026. doi: 10.1073/pnas.1303607110
52. Powter B, Jeffreys SA, Sareen H, et al. Human TERT promoter mutations as a prognostic biomarker in glioma. *Journal of Cancer Research and Clinical Oncology*. 2021;147(4):1007-1017. doi: 10.1007/s00432-021-03536-3
53. Hasanau T, Pisarev E, Kisil O, Nonoguchi N, Le Calvez-Kelm F, Zvereva M. Detection of TERT Promoter Mutations as a Prognostic Biomarker in Gliomas: Methodology, Prospects, and Advances. *Biomedicines*. 2022;10(3):728. doi: 10.3390/biomedicines10030728
54. Beylerli O, Gareev I, Sufianov A, Ilyasova T, Zhang F. The role of microRNA in the pathogenesis of glial brain tumors. *Non-coding RNA Research*. 2022;7(2):71-76. doi: 10.1016/j.ncrna.2022.02.005
55. Wang Y, Tian Y, Li Z, Zheng Z, Zhu L. miR-92 regulates the proliferation, migration, invasion and apoptosis of glioma cells by targeting neogenin. *Open Medicine*. 2020;15(1):283-291. doi: 10.1515/med-2020-0040
56. Sadegh Shirian, Yahya Daneshbod, Saranaz Jangjoo, et al. The Role of Next Generation Sequencing in Diagnosis of Brain Tumors: A Review Study. *Archives of Neuroscience*. 2019;7(1). doi: 10.5812/ans.68874
57. Sahm F, Schrimpf D, Jones DTW, et al. Next-generation sequencing in routine brain tumor diagnostics enables an integrated diagnosis and identifies actionable targets. *Acta Neuropathologica*. 2016;131(6):903-910. doi: 10.1007/s00401-015-1519-8
58. Higa N, Akahane T, Yokoyama S, et al. A tailored next-generation sequencing panel identified distinct subtypes of wildtype IDH and TERT promoter glioblastomas. *Cancer Science*. 2020;111(10):3902-3911. doi: 10.1111/cas.14597
59. Eibl RH, Schneemann M. Liquid Biopsy and Primary Brain Tumors. *Cancers*. 2021;13(21):5429. doi: 10.3390/cancers13215429
60. Jones JJ, Jones KL, Wong SQ, et al. Plasma ctDNA enables early detection of temozolomide resistance mutations in glioma. *Neuro-Oncology Advances*. 2024;6(1). doi: 10.1093/noajnl/vdae041
61. Zhang H, Yuan F, Qi Y, Liu B, Chen Q. Circulating Tumor Cells for Glioma. *Frontiers in Oncology*. 2021;11. doi: 10.3389/fonc.2021.607150
62. Meng L, Song K, Li S, Kang Y. Exosomes: Small vesicles with important roles in the development, metastasis, and treatment of breast cancer. *Membranes (Basel)*. 2022;12(8):775. doi:10.3390/membranes12080775.
63. Van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol*. 2018;19:213-228. doi:10.1038/nrm.2017.125.
64. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367. doi:10.1126/science.aau6977.
65. Lei X, Lei Y, Li JK, et al. Immune cells within the tumor microenvironment: Biological functions and roles in cancer immunotherapy. *Cancer Letters*. 2020;470:126-133. doi: 10.1016/j.canlet.2019.11.009
66. Peinado H, Zhang H, Matei IR, et al. Pre-metastatic niches: organ-specific homes for metastases. *Nature Reviews Cancer*. 2017;17(5):302-317. doi: 10.1038/nrc.2017.6
67. Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. *Cell Biosci*. 2019;9:19. Published 2019 Feb 15. doi:10.1186/s13578-019-0282-2
68. Clancy JW, Schmidtmann M, D'Souza-Schorey C. The ins and outs of microvesicles. *FASEB Bioadv*. 2021;3(6):399-406. Published 2021 Mar 4. doi:10.1096/fba.2020-00127
69. Lee Y, EL Andaloussi S, Wood MJA. Exosomes and microvesicles: extracellular vesicles for genetic information transfer and gene therapy. *Human Molecular Genetics*. 2012;21(R1):R125-R134. doi: 10.1093/hmg/dd5317
70. Kwok ZH, Wang C, Jin Y. Extracellular Vesicle Transportation and Uptake by Recipient Cells: A Critical Process to Regulate Human Diseases. *Processes (Basel)*. 2021;9(2):273. doi:10.3390/pr9020273
71. Mulcahy LA, Pink RC, Carter DR. Routes and mechanisms of extracellular vesicle uptake. *J Extracell Vesicles*. 2014;3:10.3402/jev.v3.24641. Published 2014 Aug 4. doi:10.3402/jev.v3.24641
72. Maacha S, Bhat AA, Jimenez L, et al. Extracellular vesicles-mediated intercellular communication: roles in the tumor microenvironment and anti-cancer drug resistance. *Mol Cancer*. 2019;18(1):55. Published 2019 Mar 30. doi:10.1186/s12943-019-0965-7
73. Chen J, Fei X, Wang J, Cai Z. Tumor-derived extracellular vesicles: Regulators of tumor microenvironment and the enlightenment in tumor therapy. *Pharmacol Res*. 2020;159:105041. doi:10.1016/j.phrs.2020.105041
74. Doyle LM, Wang MZ. Overview of Extracellular Vesicles, Their Origin, Composition, Purpose, and Methods for Exosome Isolation and Analysis. *Cells*. 2019;8(7):727. Published 2019 Jul 15. doi:10.3390/cells8070727
75. Banks WA, Sharma P, Bullock KM, Hansen KM, Ludwig N, Whiteside TL. Transport of Extracellular Vesicles across the Blood-Brain Barrier: Brain Pharmacokinetics and Effects of Inflammation. *Int J Mol Sci*. 2020;21(12):4407. Published 2020 Jun 21. doi:10.3390/ijms21124407
76. Meng W, He C, Hao Y, Wang L, Li L, Zhu G. Prospects and challenges of extracellular vesicle-based drug delivery system: considering cell source. *Drug Deliv*. 2020;27(1):585-598. doi:10.1080/10717544.2020.1748758
77. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood-brain barrier: structure, regulation, and drug delivery. *Signal Transduction and Targeted Therapy*. 2023;8(1):1-27. doi: 10.1038/s41392-023-01481-w
78. Shah K. Stem cell-based therapies for tumors in the brain: are we there yet?. *Neuro Oncol*. 2016;18(8):1066-1078. doi:10.1093/neuonc/now096
79. Walker S, Busatto S, Pham A, et al. Extracellular vesicle-based drug delivery systems for cancer treatment. *Theranostics*. 2019;9(26):8001-8017. Published 2019 Oct 17. doi:10.7150/thno.37097
80. Wang L, Yu X, Zhou J, Su C. Extracellular Vesicles for Drug Delivery in Cancer Treatment. *Biological Procedures Online*. 2023;25(1). doi: 10.1186/s12575-023-00220-3
81. ClinicalTrials.gov. A Study to Evaluate the Safety and Tolerability of Exosome Associated AEGIS-loaded miRNA-185 in Subjects With Glioblastoma.

82. ClinicalTrials.gov. Tumor-derived Exosomes in Lung Cancer. <https://clinicaltrials.gov/ct2/show/NCT02657460>. Published January 14, 2016. Updated May 1, 2020.
83. ClinicalTrials.gov. Pilot Study of Plasma-Derived Exosomes (PDEs) in COVID-19 Patients. <https://clinicaltrials.gov/ct2/show/NCT04394572>. Published May 20, 2020. Updated June 8, 2022.
84. ClinicalTrials.gov. Evaluation of Exosomes as Therapeutic Agents in Alzheimer's Disease. <https://clinicaltrials.gov/ct2/show/NCT02862315>. Published August 17, 2016. Updated October 10, 2019.
85. ClinicalTrials.gov. Study of Tumor-Derived Exosomes as Biomarkers in Pancreatic Cancer. <https://clinicaltrials.gov/ct2/show/NCT03468426>. Published March 16, 2018. Updated April 15, 2022.
86. ClinicalTrials.gov. Diagnostic and Prognostic Role of Exosomes in Traumatic Brain Injury. <https://clinicaltrials.gov/ct2/show/NCT03608631>. Published August 1, 2018. Updated May 1, 2022.
87. ClinicalTrials.gov. B-cell-derived Exosomes as Biomarkers in Multiple Myeloma. <https://clinicaltrials.gov/ct2/show/NCT04327470>. Published March 31, 2020. Updated April 15, 2022.
88. Wichmann TO, Damkier HH, Pedersen M. A Brief Overview of the Cerebrospinal Fluid System and Its Implications for Brain and Spinal Cord Diseases. *Front Hum Neurosci*. 2022;15:737217. Published 2022 Jan 21. doi:10.3389/fnhum.2021.737217
89. Martucci M, Russo R, Schimperna F, et al. Magnetic Resonance Imaging of Primary Adult Brain Tumors: State of the Art and Future Perspectives. *Biomedicines*. 2023;11(2):364. Published 2023 Jan 26. doi:10.3390/biomedicines11020364
90. Tumani H, Petereit HF, Gerritzen A, et al. S1 guidelines "lumbar puncture and cerebrospinal fluid analysis" (abridged and translated version). *Neurol Res Pract*. 2020;2:8. Published 2020 Mar 16. doi:10.1186/s42466-020-0051-z
91. Kadry H, Noorani B, Cucullo L. A blood-brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids Barriers CNS*. 2020;17(1):69. Published 2020 Nov 18. doi:10.1186/s12987-020-00230-3
92. Adashek JJ, Janku F, Kurzrock R. Signed in Blood: Circulating Tumor DNA in Cancer Diagnosis, Treatment and Screening. *Cancers (Basel)*. 2021;13(14):3600. Published 2021 Jul 18. doi:10.3390/cancers13143600
93. Reilly KM. Brain tumor susceptibility: the role of genetic factors and uses of mouse models to unravel risk. *Brain Pathol*. 2009;19(1):121-131. doi:10.1111/j.1750-3639.2008.00236.x
94. Das S, Dey MK, Devireddy R, Gartia MR. Biomarkers in Cancer Detection, Diagnosis, and Prognosis. *Sensors (Basel)*. 2023;24(1):37. Published 2023 Dec 20. doi:10.3390/s24010037
95. Yanez-Mó M, Siljander PR, Andreu Z, et al. Biological properties of extracellular vesicles and their physiological functions. *J Extracell Vesicles*. 2015;4:27066. Published 2015 May 14. doi:10.3402/jev.v4.27066
96. Karlsson L, Vogel J, Arvidsson I, et al. Cerebrospinal fluid reference proteins increase accuracy and interpretability of biomarkers for brain diseases. *Nature Communications*. 2024;15(1). doi: 10.1038/s41467-024-47971-5
97. Jelski W, Mroczko B. Molecular and Circulating Biomarkers of Brain Tumors. *International Journal of Molecular Sciences*. 2021;22(13):7039. doi: 10.3390/ijms22137039

How to cite this article: Nivetha Mahesh, Revanth R Emerging Biomarkers for Brain Tumors: Advances in Early Detection and Therapeutic Monitoring. *Indian J Pharm Drug Studies*. 2026; Online First.

Funding: None; Conflicts of Interest: None Stated