Glioblastoma biomarkers

- Spatial Mapping of Glioblastoma Infiltration: Diffusion Tensor Imaging-Based Radiomics and Connectomics in Recurrence Prediction
- Integrated Workflow for Drug Repurposing in Glioblastoma: Computational Prediction and Preclinical Validation of Therapeutic Candidates
- GLUT1 as a Potential Therapeutic Target in Glioblastoma
- RIPK1 in Diffuse Glioma Pathology: From Prognosis Marker to Potential Therapeutic Target
- Molecular Biomarkers of Glioma
- Epigenetic Alterations in Glioblastoma Multiforme as Novel Therapeutic Targets: A Scoping Review
- Evaluating the Antitumor Potential of Cannabichromene, Cannabigerol, and Related Compounds from Cannabis sativa and Piper nigrum Against Malignant Glioma: An In Silico to In Vitro Approach
- The Circadian Rhythm Gene Network Could Distinguish Molecular Profile and Prognosis for Glioblastoma

Glioblastoma (GBM), the most aggressive primary brain tumor, is characterized by a highly heterogeneous molecular profile. Understanding biomarkers in GBM is critical for diagnosis, prognosis, and personalized therapy.

Biomarker	Type	Frequency	Clinical Relevance	Prognosis
IDH1/IDH2 mutation	Genetic	~10% (mostly secondary GBM)	Differentiates primary vs secondary GBM	Better survival
MGMT promoter methylation	Epigenetic	~45%	Predicts response to temozolomide	Better outcome
TERT promoter mutation	Genetic	Common in primary GBM	Maintains telomere length	Poorer prognosis (context-dependent)
ATRX loss	Genetic/protein	Associated with IDH-mutant GBM	Suggests secondary GBM pathway	Better prognosis if with IDH mutation
EGFR amplification / EGFRvIII mutation	Genetic	~50%	Target for experimental therapies	Poorer prognosis
1p/19q co-deletion	Cytogenetic	Rare in GBM, common in oligodendroglioma	Diagnostic exclusion for GBM	Favourable (but not in GBM)
p53 overexpression	Protein	Often in IDH-mutant GBM	Tumor suppressor pathway disruption	Variable
GFAP	Protein (IHC)	Expressed in most GBMs	Confirms glial origin	Not prognostic
Ki-67 (MIB-1 index)	Protein (IHC)	High in GBM	Indicates proliferation rate	Higher index = worse prognosis

Molecular Subtypes (TCGA)

- **Classical**: EGFR amplification, chromosome 10 loss
- **Mesenchymal**: NF1 mutation/deletion, aggressive behavior
- **Proneural**: IDH mutation, PDGFRA abnormalities
- **Neural**: Controversial subtype, expresses neuronal markers

Emerging Biomarkers

- MicroRNAs (e.g., miR-21, miR-10b)
- Circulating tumor DNA (ctDNA)
- Exosomes and their cargo
- PD-L1 expression and immune profile

Overview of key glioblastoma biomarkers, organized by their clinical relevance

 Diagnostic Biomarkers

These help confirm the diagnosis of GBM and distinguish it from other gliomas.

Histology + Immunohistochemistry: Classical GBM shows necrosis and microvascular proliferation.

GFAP (Glial Fibrillary Acidic Protein): Marker for glial origin, not specific to GBM.

IDH1/IDH2 Mutation Status:

IDH-wildtype GBM (most common in adults >55) is the classical form.

IDH-mutant GBMs are now classified as astrocytomas (per WHO 2021).

ATRX: Loss is typical in IDH-mutant astrocytomas; retained in GBM (IDH-wt).

 Prognostic Biomarkers

These predict disease outcome irrespective of treatment.

MGMT Promoter Methylation:

Methylation = better prognosis and improved response to temozolomide.

TERT Promoter Mutations:

Common in GBM; associated with poor prognosis.

Chromosome 10q Loss and EGFR Amplification:

Linked to aggressive behavior and poor outcomes.

PTEN Mutations:

Loss of tumor suppressor function, associated with progression.

 Predictive Biomarkers

These help determine the response to specific therapies.

MGMT Promoter Methylation:

Predicts response to alkylating agents (e.g., temozolomide).

EGFR Amplification/Mutation:

EGFRvIII (variant III) is a common mutant isoform, targeted in trials (e.g., with vaccines or TKIs).

PD-L1 Expression:

Low in most GBMs, limiting immunotherapy efficacy, but under study.

Mismatch Repair Deficiency / Microsatellite Instability (MSI):

Rare in GBM but may respond to immune checkpoint inhibitors.

 Emerging and Research Biomarkers

These are under active investigation for potential future clinical application.

Circulating Tumor DNA (ctDNA) and extracellular vesicles in CSF or blood.

MET Amplification / Fusion (e.g., MET exon 14 skipping mutations).

NTRK Fusions: Rare but actionable with TRK inhibitors.

Epigenetic Signatures (e.g., DNA methylation profiling like “glioma-CIMP”).

MicroRNAs (e.g., miR-21, miR-10b): Under research as diagnostic and prognostic tools.

MGMT promoter-methylated glioblastoma

MGMT promoter-methylated glioblastoma

Epidermal growth factor receptor 3 in glioblastoma

Epidermal growth factor receptor 3 in glioblastoma

More and more biomarkers continue to be identified in glioblastoma Glioblastoma patients. Such biomarkers are related with varying degrees of specificity to one or more of Glioblastoma's subtypes and, in many instances, may provide useful information about prognosis. Biomarkers fall into either the imaging or molecular category. Molecular biomarkers are identified by use of such platforms as genomics, proteomics, and metabolomics. In the future, biomarkers, either individually or in some combination, will more reliably identify the pathogenic type of Glioblastoma and determine choice of therapy [1)].

Molecular biomarkers have become an integral part of tumor assessment in modern neuro-oncology and biomarker status now guides clinical decisions in some subtypes of gliomas, including anaplastic oligodendroglioma and glioblastoma in the elderly.

In gliomas molecular biomarkers are increasingly gaining diagnostic, prognostic and predictive significance. Determination of biomarker status after biopsy is important as not all patients are eligible for open tumor resection.

159 consecutively enrolled untreated gliomas were analyzed (94 glioblastomas, 2 gliosarcomas, 24 anaplastic astrocytomas, 10 oligo-tumors grade II/III, 20 grade II astrocytomas and 9 pilocytic astrocytomas). Transient morbidity was 2 %. Overall, the drop-out rate due to tissue contamination was 0.4 %. Median time from biopsy to histological and molecular genetic analyses was 3 and 5 days, respectively. Distributions of the respective biomarker status for tumor subgroups were consistent with the literature. The final histological diagnosis was changed/modified in 5/159 patients according to molecular findings. Treatment after molecular biopsy was highly

Molecular stereotactic biopsy is feasible and safe, can be implemented in daily clinical practice, improves diagnostic precision and enables personalized treatment [2)].

Advances in the understanding of the molecular biology of glioblastoma are being rapidly translated into innovative clinical trials, capitalizing on improved genomic, epigenetic, transcriptional, and proteomic characterization of glioblastomas as well as host factors, including the brain microenvironment and immune system interactions.

Biomarker discovery studies are needed to predict treatment outcome for patients with Glioblastoma [3)].

Aberrant gene expression and copy number alterations make it possible to identify four subtypes: classical, mesenchymal, proneural, and neural. More and more biomarkers continue to be identified in glioblastoma (Glioblastoma) patients. Such biomarkers are related with varying degrees of specificity to one or more of Glioblastoma's subtypes and, in many instances, may provide useful information about prognosis. Biomarkers fall into either the imaging or molecular category. Molecular biomarkers are identified by use of such platforms as genomics, proteomics, and metabolomics. In the future, biomarkers, either individually or in some combination, will more reliably identify the pathogenic type of Glioblastoma and determine choice of therapy.

Understanding the important biomarkers that play a role in Glioblastoma pathogenesis may also help clinicians in educating patients about prognosis, potential clinical trials, and monitoring response to treatments [4)].

In a study, dataset GSE50161 was used to construct a co-expression network for weighted gene co-expression network analysis. Two modules (dubbed brown and turquoise) were found to have the strongest correlation with glioblastoma (Glioblastoma). Functional enrichment analysis indicated that the brown module was involved in the cell cycle, DNA replication, and pyrimidine metabolism. The turquoise module was primarily related to circadian rhythm entrainment, glutamatergic synapses, and axon guidance. Hub genes were screened by survival analysis using The Cancer Genome Atlas and Human Protein Atlas databases and further tested using the GSE4290 and Gene Expression Profiling Interactive Analysis databases. The eight hub genes (NUSAP1, SHCBP1, KNL1, SULT4A1, SLC12A5, NUF2, NAPB, and GARNL3) were verified at both the transcriptional and translational levels, and these gene expression levels were significant based on the World Health Organization classification system. These hub genes may be potential biomarkers and therapeutic targets for the accurate diagnosis and management of Glioblastoma [5].

A study of Zhao et al. aimed to identify novel tumor biomarkers with independent prognostic values in Glioblastomas. The DNA methylation profiles were downloaded from The Cancer Genome Atlas and Gene Expression Omnibus database. Differential methylated genes (DMGs) were screened from Glioblastoma recurrence samples using limma package in R software. Functional enrichment analysis was performed to identify major biological processes and signaling pathways. Furthermore, critical DMGs associated with glioblastoma outcome were screened according to univariate and multivariate cox regression analysis. A risk score-based prognostic model was constructed for these DMGs and prediction ability of this model was validated in training dataset and validation dataset. In total, 495 DMGs were identified between recurrent samples and disease-free samples, including 356 significantly hypermethylated and 139 hypomethylated genes. Functional and pathway items for these DMGs were mainly related to sensory organ development, neuroactive ligand-receptor interaction, pathways in cancer, etc. Five genes with abnormal methylation level were significantly correlated with prognosis according to survival analysis, such as ALX1, KANK1, NUDT12, SNED1, and SVOP. Finally, the risk model provided an effective ability for prognosis prediction both in training and validation data set. They constructed a novel prognostic model for survival prediction of Glioblastomas. In addition, they identified five DMGs as critical prognostic biomarkers in Glioblastoma progression [6].

p53

Platelet-derived growth factor receptor (PDGFR)

Phosphatase and tensin homolog (PTEN)

Phosphoinositide 3-kinase (PI3K)

1p/19q.

Translational exploratory proteomics studies

In a Translational Exploratory Proteomics Study, Liu et al. introduce the Nano-omics integrative

workflow that links systemic (plasma) and localised (tumour tissue) protein changes associated with glioblastoma progression. Mass spectrometry analysis of the nanoparticle biomolecule corona in GL261-bearing mice at different stages of GB revealed plasma protein alterations, even at low tumour burden, with over 30% overlap between GB-specific plasma and tumour tissue proteomes. Analysis of matched plasma and surgically resected tumour samples from high-grade glioma patients demonstrates the clinical applicability of the Nano-omics pipeline. Cross-species correlation identified 48 potential glioblastoma biomarker candidates involved in actin cytoskeleton organisation, focal adhesion, platelet activation, leukocyte migration, amino acid biosynthesis, carbon metabolism, and phagosome pathways. The Nano-omics approach holds promise for the discovery of early detection and disease monitoring biomarkers of central nervous system conditions, paving the way for subsequent clinical validation [7)]

Liu et al. present an innovative Nano-omics integrative proteomics pipeline that links systemic (plasma) and localized (tumour tissue) protein changes associated with glioblastoma (GB) progression. The authors perform **mass spectrometry** analysis of the **biomolecule corona** formed on nanoparticles injected into **GL261-bearing mice**, uncovering alterations in plasma proteins even in the early stages of tumour development. Notably, over 30% of the **proteomic signatures** overlap between plasma and tumour tissue in these murine models.

The authors extend their findings to a clinical context by analysing **matched plasma and surgically resected tumour samples** from patients with high-grade glioma. This cross-species approach results in the identification of **48 potential GB biomarker candidates**, linked to key biological pathways including actin cytoskeleton organisation, focal adhesion, platelet activation, leukocyte migration, amino acidbiosynthesis, carbon metabolism, and phagosome pathways.

This study is a **translational proteomics** investigation, with elements of **comparative analysis** and **biomarker discovery** across species. It cleverly leverages the **nanoparticle protein corona** phenomenon as a biological readout of disease states, thereby extending the potential of liquid biopsy in brain tumours—a notoriously difficult domain for early detection.

The study's strengths lie in its cross-species validation, the integration of multi-tissue omics, and the real-world applicability demonstrated through patient samples. Importantly, the study bridges the gap between preclinical findings and clinical biomarker development, something many high-impact papers fail to achieve.

However, several **limitations** must be considered:

- The **GL261 mouse model** is widely used but does not fully replicate the genetic and microenvironmental heterogeneity of human GB.
- The **sample size** for the clinical arm is not specified in the abstract and may limit statistical power.
- While the proteomic overlap is promising, **functional validation** of these 48 biomarker candidates remains to be done.
- The specificity of these markers to GB versus other brain or systemic inflammatory diseases is not assessed.

Overall, Liu et al.'s study represents a **proof-of-concept** investigation and should be followed by larger **clinical validation studies**. The Nano-omics pipeline is a promising tool that might contribute to future glioblastoma diagnosis and biomarker development for central nervous system disorders.

This is a **translational, exploratory proteomics study** that combines **preclinical experimental models** with **human clinical samples** to identify potential biomarkers for glioblastoma. It is a non-randomized hypothesis-generating study in nature.

Publications

Zachariah M, Oliveira-Costa JP, Carter B, Stott SL, Nahed BV. Blood-Based Biomarkers for the Diagnosis and Monitoring of Gliomas. Neuro Oncol. 2018 May 9. doi: 10.1093/neuonc/noy074. [Epub ahead of print] PubMed PMID: 29746665 [8].

1)
Nicolaidis S. Biomarkers of glioblastoma multiforme. Metabolism. 2014 Oct 30. pii: S0026-0495(14)00340-0. doi: 10.1016/j.metabol.2014.10.031. [Epub ahead of print] PubMed PMID: 25468141.

2)
Eigenbrod S, Trabold R, Brucker D, Erös C, Egensperger R, La Fougere C, Göbel W, Rühm A, Kretzschmar HA, Tonn JC, Herms J, Giese A, Kreth FW. Molecular stereotactic biopsy technique improves diagnostic accuracy and enables personalized treatment strategies in glioma patients. Acta Neurochir (Wien). 2014 Aug;156(8):1427-40. doi: 10.1007/s00701-014-2073-1. Epub 2014 May 3. PubMed PMID: 24792966.

3)
van Linde ME, van der Mijn JC, Pham TV, Knol JC, Wedekind LE, Hovinga KE, Aliaga ES, Buter J, Jimenez CR, Reijneveld JC, Verheul HM. Evaluation of potential circulating biomarkers for prediction of response to chemoradiation in patients with glioblastoma. J Neurooncol. 2016 Sep;129(2):221-30. doi: 10.1007/s11060-016-2178-x. Epub 2016 Jul 21. PubMed PMID: 27444431; PubMed Central PMCID: PMC4992035.

4)
Karsy M, Neil JA, Guan J, Mark MA, Colman H, Jensen RL. A practical review of prognostic correlations of molecular biomarkers in glioblastoma. Neurosurg Focus. 2015 Mar;38(3):E4. doi: 10.3171/2015.1.FOCUS14755. PubMed PMID: 25727226.

5)
Li C, Pu B, Gu L, Zhang M, Shen H, Yuan Y, Liao L. Identification of key modules and hub genes in glioblastoma multiforme based on co-expression network analysis. FEBS Open Bio. 2021 Jan 10. doi: 10.1002/2211-5463.13078. Epub ahead of print. PMID: 33423377.

6)
Zhao J, Wang L, Kong D, Hu G, Wei B. Construction of Novel DNA Methylation-Based Prognostic Model to Predict Survival in Glioblastoma. J Comput Biol. 2019 Aug 28. doi: 10.1089/cmb.2019.0125. [Epub ahead of print] PubMed PMID: 31460783.

7)
Liu X, Abmanhal-Masarweh H, Iwanowytsch O, Okwelogu E, Arashvand K, Karabatsou K, Ivo D'Urso P, Roncaroli F, Kostarelos K, Kisby T, Hadjidemetriou M. Plasma-to-tumour tissue integrated proteomics using nano-omics for biomarker discovery in glioblastoma. Nat Commun. 2025 Apr 10;16(1):3412. doi: 10.1038/s41467-025-58252-0. PMID: 40210624.

8)
Zachariah M, Oliveira-Costa JP, Carter B, Stott SL, Nahed BV. Blood-Based Biomarkers for the Diagnosis and Monitoring of Gliomas. Neuro Oncol. 2018 May 9. doi: 10.1093/neuonc/noy074. [Epub ahead of print] PubMed PMID: 29746665.