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Multi-Omics Integration for Advancing Glioma Precision Medicine

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ABSTRACT

Gliomas are among the most malignant and aggressive tumors of the central nervous system, characterized by the absence of early diagnostic markers, poor prognosis, and a lack of effective treatments. Advances in high-throughput technologies have facilitated a refined molecular classification of gliomas, incorporating genetic features. However, diagnosis and clinical management based on isolated genetic data often fail to capture the full histological and molecular complexity of these tumors, posing significant challenges. In the era of computational methodologies and artificial intelligence, the integration of multiple omics layers—genomics, transcriptomics (including sex-dependent differential expression patterns), epigenomics, proteomics, metabolomics, radiomics, single-cell analysis, and spatial omics—into a comprehensive framework holds the potential to deepen our understanding of glioma biology and enhance diagnostic precision, prognostic accuracy, and treatment efficacy. Herein, we provide a comprehensive overview of multi-omics strategies used to decipher the adult-type diffuse glioma molecular taxonomy and describe how the integration of multilayer data combined with machine-learning-based algorithms is paving the way for advancements in patient prognosis and the development of personalized, targeted therapeutic interventions.

1 | Introduction

Gliomas are the most common primary brain tumors arising from glial cells of the central nervous system (CNS), with a global incidence of approximately 3.8 to 4.4 cases per 100,000 people annually for all gliomas (24,820 new cases in the US), and an incidence of about 3.3 to 3.9 per 100,000 for glioblastoma (12,000 new cases in the US), the most common and deadly glioma subtype [1]. Known by their infiltrative nature and heterogeneity,

these types of malignancies span a broad spectrum of conditions classified into four grades of malignancy according to the CNS World Health Organization (WHO) system, each presenting distinct diagnostic and therapeutic challenges [2].

Clinically, gliomas manifest through a wide range of symptoms, often dictated by their location in the brain, including headaches, seizures, focal neurological deficits, and cognitive impairments [3, 4]. Diagnosis relies on a combination of neuroimaging

Abbreviations: CL, classical; CNS, central nervous system; CNVs, copy number variants; CT, computed tomography; DME, DNA methylation-expressed; EGFR, epidermal growth factor receptor; GBM, glioblastoma; LGG, low-grade gliomas; MES, mesenchymal; MRI, magnetic resonance imaging; OS, overall survival; OXPHOS, oxidative phosphorylation; pd-GBSC, patient-derived GBM stem cell; PET, positron emission tomography; PN, proneural; scRNA-seq, single-cell transcriptomics; SNVs, single nucleotide variants; SPHINKS, Substrate PHosphosite-based Inference for Network of KinaseS; TCGA, The Cancer Genome Atlas; VEGF, vascular endothelial growth factor; WHO, World Health Organization.

Maria Guarnaccia and Valentina La Cognata contributed equally to this study.

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techniques—magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography (PET)—complemented by histopathological analysis obtained through surgical biopsy or tumor resection [5, 6]. Treatment strategies embrace a multidisciplinary approach, incorporating surgical resection to reduce tumor burden and relieve mass effect, along with adjuvant therapies such as radiotherapy and chemotherapy to target residual tumor cells and mitigate disease recurrence [7]. The advent of molecularly targeted agents, such as the inhibitors of the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), is providing some innovative avenues for tailored treatment selection and personalized therapeutic interventions [8, 9], offering both challenges and opportunities in accurately diagnosing, classifying, and managing gliomas.

The emergence of Omics Sciences and the development of The Cancer Genome Atlas (TCGA) have significantly improved the ability to distinguish different layers of glioma heterogeneity, leading to a revised WHO classification system that integrates multiple molecular profiles, including DNA methylation patterns, gene expression signatures, and mutational landscapes. According to the latest classification, the prognosis and treatment of gliomas vary significantly depending on the glioma type—such as astrocytoma, IDH-mutant (grades 2, 3, or 4), oligodendroglioma, IDH-mutant with 1p/19q codeletion (grades 2 or

3), and glioblastoma, IDH-wildtype (grade 4)—as well as on molecular markers including IDH1/2, H3-3A, ATRX, CDKN2A/B, 1p/19q codeletion, TERT promoter mutations, MGMT promoter methylation, EGFR amplifications, PTEN deletions, and BRAF alterations [10, 11].

While single-omics approaches offer a limited view that fails to fully capture the tumor's diverse histological, cellular, and molecular characteristics, modern computational methods and artificial intelligence-driven technologies are facilitating the integration of multiple omics layers—genomics, transcriptomics, epigenomics, proteomics, metabolomics, radiomics, and single-cell analysis—providing a holistic perspective on glioma biology. This multidimensional approach enhances diagnostic precision, refines prognostic predictions, and improves therapeutic outcomes (Figure 1) [12–14]. The growing adoption of integrative omics strategies is uncovering previously unknown molecular relationships, pathways, and biological processes. The linkage of these findings with patient-specific clinical data is emerging as a critical step toward identifying molecular signatures that hold significant potential for personalized medicine and individualized treatment approaches (Figure 1).

In this work, we provide a comprehensive overview of the role of multi-omics methodologies in glioma research and explore how

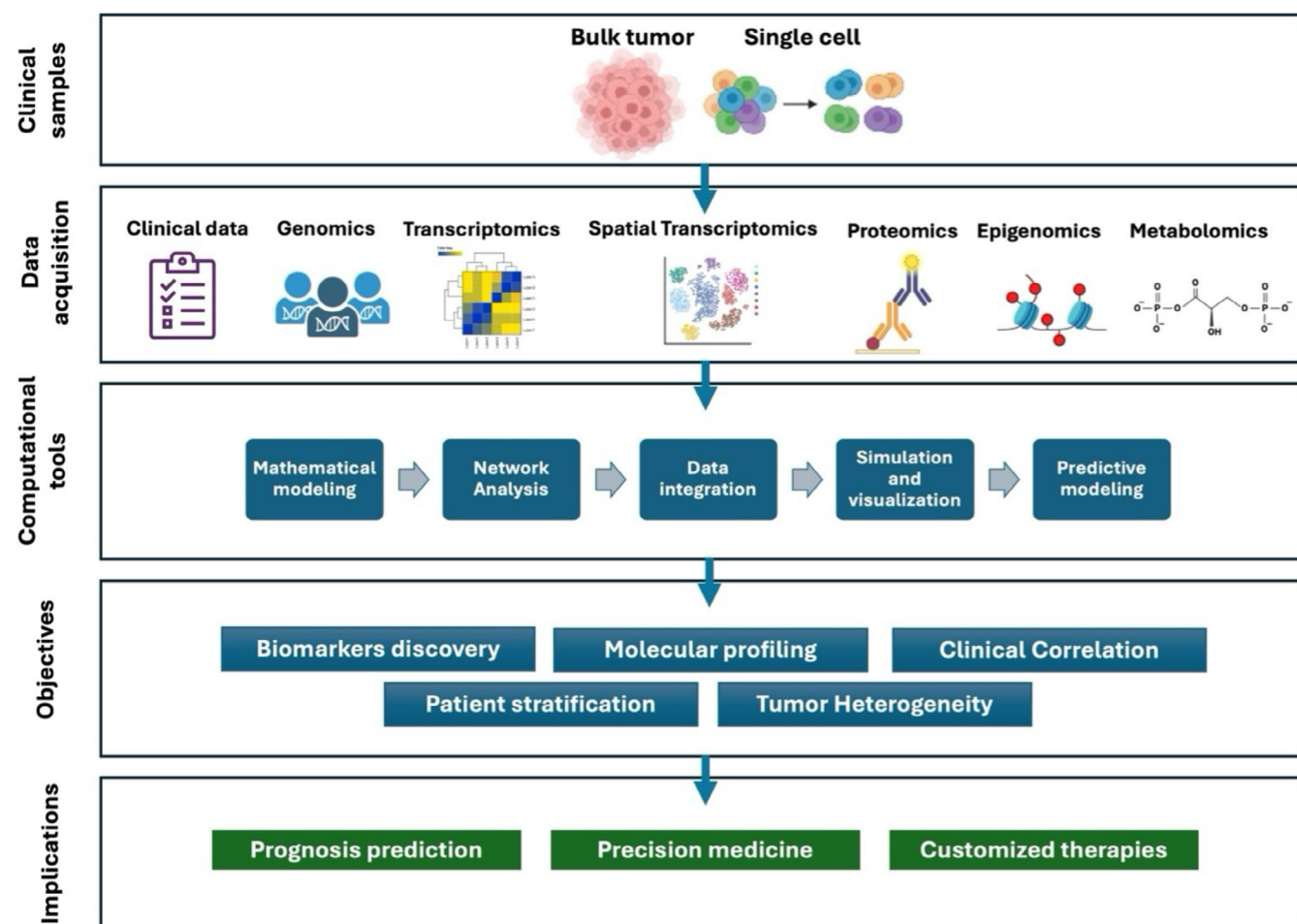


FIGURE 1 | Integrative multi-omics and network systems modeling in gliomas. Schematic representation of how multi-omics datasets can be integrated by computational tools to achieve a comprehensive understanding of glioma biology. This approach enables the identification of key molecular drivers, subtype-specific vulnerabilities, prognostic biomarkers, and potential therapeutic targets.

the integration of multilayered data is advancing glioma taxonomy, prognosis and personalized therapeutic strategies.

2 | Molecular Classification of Adult Type Diffuse Gliomas: State of Art

Accurately grading gliomas remains a significant challenge, as their pathogenesis results from the accumulation of malignant genetic alterations that define distinct molecular subtypes associated with specific clinical features [15–17]. Imaging plays a pivotal role in glioma diagnosis, with contrast-enhanced CT and MRI serving as the primary modalities for initial assessment and staging [18]. CT is commonly utilized in emergency settings as the first-line imaging tool to rapidly evaluate brain lesions, hemorrhages, calcifications, and acute complications [19], whereas MRI provides detailed visualization of tumor boundaries, edema, and interactions with surrounding brain tissue [20]. Advanced MRI techniques further enhance diagnostic precision by offering integrated anatomical, functional, and metabolic insights [21].

The integration of traditional histopathological criteria with genetic and molecular biomarkers has recently reshaped glioma classification, advancing toward a personalized medicine approach. The revised WHO 2021 classification (Figure 2) had a profound impact on clinical management, categorizing primary gliomas into grades 1 to 4, corresponding to low-grade gliomas (LGG) and high-grade gliomas (HGG). Specifically, these include: Pilocytic astrocytoma (CNS WHO grade 1); Oligodendroglioma, *IDH*-mutant and 1p/19q-codeleted (CNS WHO grades 2 and 3); Astrocytoma, *IDH*-mutant (CNS WHO grade 3); Astrocytoma, *IDH*-mutant with *CDKN2A/B* homozygous deletion (CNS WHO grade 4); Glioblastoma,

IDH-wildtype (CNS WHO grade 4); and Glioblastoma, *IDH*-wildtype with *TERT* promoter mutation, *EGFR* amplification, or chromosome 7 gain/chromosome 10 loss (CNS WHO grade 4) [22, 23].

Moreover, glioblastoma (GBM) is further classified into three transcriptional subtypes—proneural (PN), mesenchymal (MES) and classical (CL)—or, in patient-derived glioma cell line models, into PN, MES and OXPHOS subtypes, each characterized by distinct molecular alterations, therapeutic sensitivities, and prognostic implications [24, 25]. Recent studies have also described hybrid and transitional glioma subtypes, exhibiting mixed transcriptional profiles and intermediate phenotypes [26], highlighting the dynamic nature of glioma biology and the existence of transitional states between molecular subgroups [27].

Numerous investigations have identified additional genetic alterations and biological markers that inform tumor classification [28–32], glioma differentiation, disease progress estimation [33], patient survival assessment and therapeutic response prediction [2, 34, 35]. Currently, the “My Cancer Genome” tool (<https://www.mycancergenome.org>) catalogs a broad spectrum of genetic biomarkers—including Single Nucleotide Variants (SNVs), Copy Number Variants (CNVs), structural rearrangements, protein expression markers, chromosomal aberrations and genomic instability indicators—associated with different glioma types. Many of these biomarkers are actively used for diagnosis, prognosis and treatment selection and are linked to ongoing clinical trials [36, 37] (Figure 3).

The molecular markers of each glioma subtype further influence prognosis and are critical for guiding treatment strategies. In LGG, key alterations include *IDH1/2*, *TP53* and *ATRX* mutations in Astrocytoma and 1p/19q co-deletions in

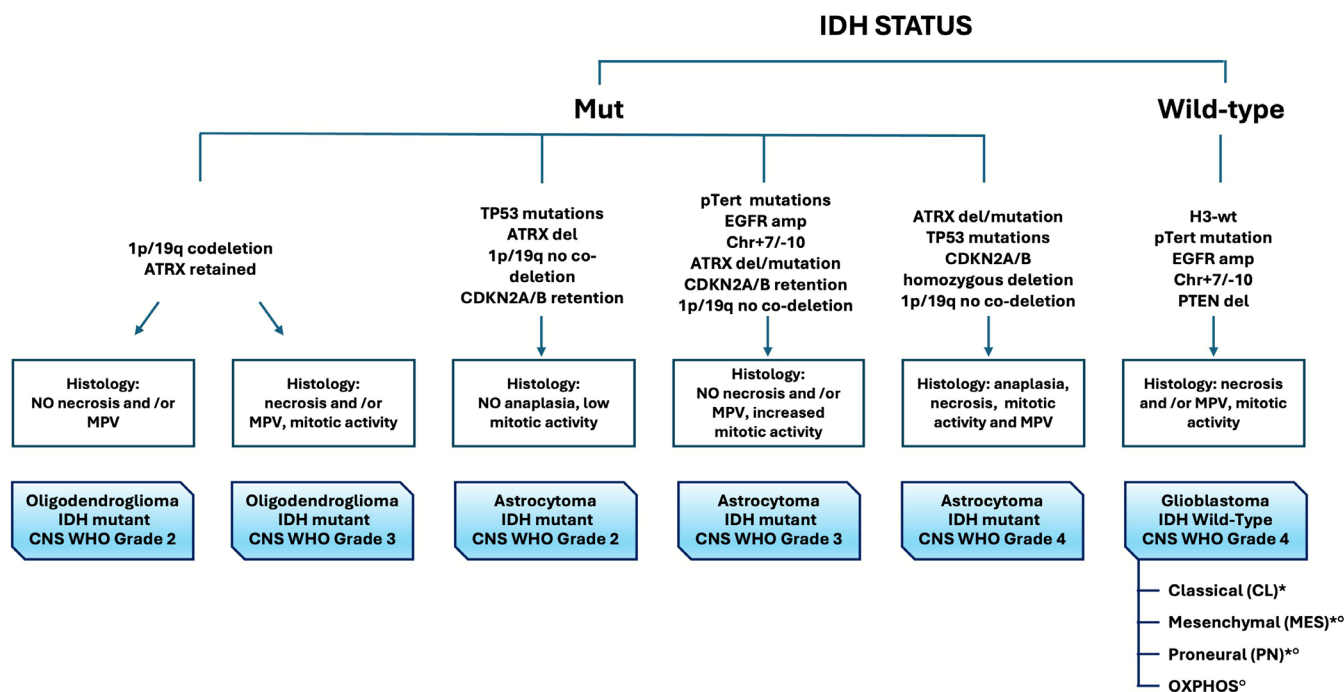
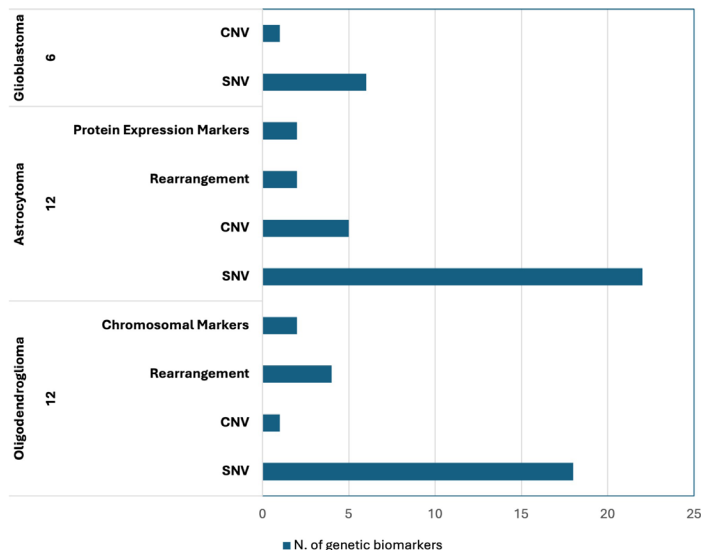


FIGURE 2 | The 2021 WHO classification of gliomas, integrating histopathological features and molecular markers. MPV, microvascular proliferation; transcriptional subtypes (*); patient-derived glioma cell lines subtypes (°).



Genetic Biomarker	Type of Gliomas	Impact	Main Use
IDH1/IDH2	Oligodendroglioma/ Astrocytoma	Improved survival, favorable prognosis	Diagnosis, Prognosis, Therapy
1p/19q Co-deletion	Oligodendroglioma	Better therapy response, favorable prognosis	Diagnosis, Prognosis
TERT Promoter	Astrocytoma/ Glioblastoma	Variable prognosis, often unfavorable without therapy	Diagnosis, Prognosis
MGMT Methylation	Glioblastoma	Better response to temozolomide, favorable prognosis	Prognosis, Therapy
EGFR	Oligodendroglioma/ Astrocytoma/Glioblastoma	Unfavorable prognosis, tumor aggressiveness	Diagnosis, Prognosis, Therapy
TP53	Astrocytoma	Poor prognosis, resistance to therapies	Diagnosis, Prognosis, Therapy
ATRX	Astrocytoma	Better prognosis	Diagnosis, Prognosis
CDKN2A	Astrocytoma	Poor prognosis	Diagnosis, Prognosis
PTEN	Glioblastoma	Poor prognosis	Prognosis
FGFR11/2/3/4	Oligodendroglioma/ Astrocytoma	Poor prognosis, resistance to therapies	Prognosis, Therapy
RB1	Astrocytoma	Poor prognosis	Prognosis
NF1	Oligodendroglioma/ Astrocytoma/Glioblastoma	Poor prognosis	Prognosis, Therapy
PDGFRA	Astrocytoma/ Glioblastoma	Poor prognosis	Prognosis, Therapy
BRAF	Oligodendroglioma/ Astrocytoma	Variable prognosis	Prognosis, Therapy
PIK3CA	Glioblastoma	Poor prognosis	Prognosis

FIGURE 3 | Glioma genetic biomarkers from “My Cancer Genome”. The histogram displays genetic biomarkers in different glioma types currently listed in “My Cancer Genome” (accessed October 2025). The accompanying table summarizes the key genetic biomarkers utilized for diagnosis, prognosis or treatment in specific glioma subtypes.

Oligodendroglioma. Generally, *IDH* mutation and retained *ATRX* expression correlate with better survival, whereas *TP53* mutations are often associated with poorer clinical outcomes, including therapy resistance and reduced survival. The presence of 1p/19q co-deletion strongly predicts a favorable prognosis [38, 39].

In HGG, *IDH* mutations are also linked to improved prognosis and longer survival, whereas *CDKN2A* deletions, Histone H3 and *TP53* mutations are associated with poor outcomes [23]. *TERT* promoter (*TERTp*) alterations typically indicate a higher risk of recurrence and worse survival in both *IDH*-wildtype and *IDH*-mutant patients. However, when *TERTp* alterations co-occur with *IDH* mutations, 1p/19q co-deletion, and *MGMT* promoter methylation, they are associated with a favorable prognosis [40, 41]. *EGFR* alterations, particularly amplifications, generally predict worse survival in astrocytomas and glioblastomas, while *PTEN* alterations (mutations or deletions) are linked to poor prognosis specifically in GBM [42, 43].

3 | Integrative Multi-Omics Data for Glioma Molecular Taxonomy and Diagnosis

The integration of extensive biological data across multiple omics layers provides significant opportunities to refine our understanding of glioma pathogenesis and enhances diagnostic accuracy [44–46]. A range of computational tools and bioinformatics resources have been developed to support glioma diagnosis and research. For example, the *GlioMarker Database* offers clinicians and researchers access to glioma diagnostic biomarkers, clinical data, and genomic expression profiles [47]. The *IPD-Brain Dataset* provides histopathological images with detailed clinical annotations and is frequently used to train deep-learning models for glioma subtype classification and biomarker prediction [48]. *Glioma-BioDP* consolidates gene, protein, histological, surgical status and survival data from low- and high-grade glioma patient samples within the TCGA database [49].

Another valuable resource, the *Surveillance Epidemiology and End Results (SEER)* database provides population-based cancer statistics for glioma risk prediction and treatment evaluation [50].

Several studies have demonstrated the utility of integrating genomic, epigenomic, and transcriptomic data with histopathological and clinical datasets to improve glioma prognosis predictions. For instance, Wu et al. developed a risk score model based on DNA methylation-expressed (DME) gene profiles from 259 glioma samples (WHO grades I–III, TCGA database) and identified six DME genes (*EMP3*, *DDIT4L*, *MEOX2*, *OCIAD2*, *TGFB2*, *TNFRSF12A*) associated with survival outcomes [51]. Similarly, Munquad et al. applied deep-learning approaches to transcriptomic and methylome data from TCGA glioma patients, achieving 98.03% accuracy in predicting LGG (astrocytoma, oligoastrocytoma, oligodendroglioma) and GBM (classical, mesenchymal, proneural) subtypes, with sensitivity above 92% [52, 53]. Binder et al. further employed Self-Organizing Maps (SOM) to classify LGG samples into distinct clusters based on integrated omics layers, revealing unique biological characteristics [46].

More recently, Vieira et al. combined mRNA, DNA methylation, and miRNA data from TCGA, using the DIABLO method, a supervised sparse canonical correlation analysis approach, to identify highly correlated molecular features distinguishing GBM from LGGs. These analyses linked GBM to receptor tyrosine kinase signaling disruptions and extracellular matrix remodeling [54]. Other studies have leveraged omics integration to uncover biomarkers associated with inflammation, mitochondrial signaling, angiogenesis, and metabolism, as well as miRNA and metabolites implicated in GBM progression [55]. Additionally, the integration of transcriptomic, miRNA, and DNA methylation datasets has enabled LGG clustering according to distinct survival trajectories [56].

Further research has uncovered novel subgroups within oligodendroglial tumors, displaying varying levels of clinical

and molecular aggressiveness [57]. Large-scale multi-omics integration studies by Jang et al. identified sex-specific genetic determinants in GBM, uncovering differences in enriched signaling pathways, treatment responses, and overall survival (OS) [58, 59]. Finally, AI-driven deep-learning frameworks and tensor analysis techniques have been employed to extract key glioma biomarkers and stratify patients based on survival outcomes [60].

4 | Integrative Multi-Omics Approaches for Glioma Prognosis Prediction

The integration of omics data with artificial intelligence (AI) and machine learning (ML) algorithms is driving advances in predicting glioma prognosis. By employing a multi-omics framework, researchers have developed models that incorporate genomic, transcriptomic, epigenomic, proteomic, and clinical data to enhance survival prediction accuracy.

For instance, Yang et al. constructed a multivariate Cox proportional hazards model for GBM and LGG patients, integrating five feature types: genetic, cytogenetic, transcriptomic, demographic, and pathologic variables. Their findings indicated that transcriptomic data served as the most informative molecular predictor of survival, while combining all variables achieved the highest accuracy [61]. Similarly, Wang et al. designed a recurrence-related signature using multi-omics data from primary and recurrent gliomas [62]. By applying LASSO regression to 108 prognostic genes, they identified an 18-gene signature that stratified patients into high- and low-risk groups, with the high-risk group exhibiting shorter overall survival (OS) and earlier recurrence [62]. Other integrative models have incorporated pseudouridine levels [63], immune-associated markers [64], and cell death profiles [65] for prognosis prediction.

Predicting survival in LGGs is particularly challenging due to their variable clinical trajectories, ranging from stable disease to rapid progression into GBM. To address this, Choi and Lee introduced Multi-Prognosis Estimation Network (Multi-PEN), a deep-learning model integrating multi-omics and multimodal data. This approach identified *MYBL1* and hsa-mir-421 as key prognostic markers, with high *MYBL1* expression and elevated miR-421 correlating with favorable outcomes [66–68]. Consequently, *MYBL1* has been incorporated as a biomarker in the 2021 WHO classification. Additionally, Du et al. combined whole-exome sequencing (WES), RNA sequencing, and DNA methylation analysis to develop a multi-omics model distinguishing LGG patients with shorter versus longer survival in both training and validation cohorts [12]. Cao et al. introduced GInLncSig, a genomic stability-based signature derived from somatic mutation and long noncoding RNA (lncRNA) data, identifying five lncRNAs whose lower risk scores predicted favorable prognosis in LGG patients [69, 70]. Similarly, Yang et al. integrated DNA methylation, copy number variation, and miRNA expression to classify LGGs into four molecularly distinct clusters (IC1–IC4), each exhibiting unique immune-related signatures, prognostic trajectories, and clinical-genetic correlations [71]. Despite histological similarity, these clusters differ in 1p/19q co-deletion (IC1 and IC2), *MGMT* promoter methylation

(IC2), *TERT* status, and mutational spectra of *IDH1*, *TP53*, and *EGFR*, translating into distinct survival outcomes [71].

Prognostic modeling of GBM remains particularly complex due to its aggressive progression and poor survival. Nassani et al. integrated gene expression, proteomics, and clinical metrics to identify molecular features associated with extended survival (6 months vs. 2 years) and improved Karnofsky performance scores (KPS). Using an iterative random forest (iRF) algorithm, they identified 35 molecular features (19 genes and 16 proteins) linked to GBM prognosis [72]. More recently, multi-omics models combining histopathological image features with genomics, transcriptomics, and proteomics achieved high predictive performance for OS, with AUCs up to 0.926 for 3-year survival prediction, demonstrating robust risk stratification capabilities [73].

5 | Integrative Multi-Omics Approaches for Personalized Targeted Treatment of Gliomas

Despite the extensive molecular characterizations of gliomas, substantial therapeutic improvements for patient outcomes remain elusive. However, integrating multi-omics data is unlocking new opportunities for personalized medicine, allowing the identification of specific molecular alterations that can guide disease management.

Migliozzi et al. developed Substrate PHosphosite-based Inference for Network of KinaseS (SPHINKS), a machine-learning algorithm integrating proteomics and phospho-proteomics data into a single network. SPHINKS enables unbiased identification of subtype-specific master kinases driving glioblastoma phenotypes. In subtype-matched GBM organoids, PKC δ and DNA-PKcs were validated as master kinases for the glycolytic/plurimetabolic (GPM) and proliferative/progenitor (PPR) subtypes, highlighting them as promising therapeutic targets [74].

Another innovative approach, i-Modern, is an integrated multi-omics deep learning network capable of accurately stratifying patients into high-risk and low-risk subgroups. Leveraging mRNA, miRNA, DNA methylation, somatic mutations, CNVs, and protein expression data, i-Modern identifies survival-associated molecular signatures while reducing high-dimensional data to informative features [75]. Top-ranked signatures included 10 gene expression, 29 CNV, 29 methylation, 9 protein, and 3 miRNA signatures, highlighting therapeutic targets such as CD276 and TGFB1 [75].

Santamarina-Ojeda et al. performed genome-wide transcriptomic and DNA methylation analyses on bulk GBM tumors and patient-derived GBM stem cells (pd-GBSCs) [76]. Integrated analyses revealed distinct pathways regulated by *AP-1*, *SMAD3*, and *RUNX1/2*, and inhibiting these pathways—alone or combined with temozolomide—significantly impaired tumor growth, particularly in aggressive mesenchymal-like GBM [76].

Wu et al. integrated genomic, transcriptomic, and drug response data to classify patient-derived glioma cell lines (PDGCs) into MES, PN, and OXPHOS subtypes, preserving key GBM driver alterations [77]. Drug screening for 214 FDA-approved compounds revealed subtype-specific vulnerabilities: PN was

sensitive to tyrosine kinase inhibitors, OXPHOS to histone deacetylase inhibitors, oxidative phosphorylation inhibitors, and HMG-CoA reductase inhibitors, while MES exhibited higher drug resistance [77].

Aberrant glycosylation contributes to tumor progression, metastasis, and therapy resistance. Strategies targeting glycosylation, using lectins, sialoglycans, glycosyltransferase inhibitors, and glycosidase inhibitors, are emerging to enhance immunotherapy efficacy [78, 79]. Forty-four glycosylation regulators have been associated with glioma survival, and seven genes were linked to high-risk patients. Glycosylation-related targets are being investigated for diagnosis (PSCA, GnT-III, sPTPRZ, Galectin-3) and prognosis (TXNDC12, PLAUR, GALNT), while glycosylated proteins such as PTPRZ, dg-Bcan-targeting peptide (BTP), and nucleolin gp273 represent potential therapeutic targets. In LGG patients, aberrant glycosylation in eight genes demonstrated predictive value for prognosis and therapy response [80, 81].

Several clinical trials (SHIVA, MOSCATO 01, ProfILER, I-PREDICT, WINTHER) evaluated matched versus unmatched therapy based on next-generation sequencing and comparative genomic hybridization. Some studies reported limited benefits due to unavailable drugs or insufficient modeling of tumor biology, while others demonstrated improved OS and progression-free survival [82]. Yi Ding et al., developed a GloMICS prognostic model, analyzing ECM-related genes across CGGA and TCGA-GBM datasets to predict OS. This model accurately predicted survival at multiple time points and can guide personalized treatment decisions [83]. Yang et al. applied single-cell RNA-seq and snATAC-seq to identify a mesenchymal GBM subtype with poor prognosis, predicting sensitivity to Trametinib and Dasatinib, validated in vitro [84]. A 2025 study identified AEBP1 and EFEMP2 as regulators of immune heterogeneity in GBM, informing immunotherapy strategies [85]. AI-driven frameworks now integrate genomic, transcriptomic, epigenomic, and radiomic data for subtype classification and drug prioritization, exemplifying the transformative potential of multi-omics in glioma precision medicine [86].

Collectively, these approaches demonstrate that multi-omics integration can identify cancer cell vulnerabilities, stratify patients for targeted therapies, and advance the precision medicine paradigm in glioma treatment.

6 | Spatial Omics as an Additional Informative Layer in Gliomas

Traditional bulk molecular techniques have been instrumental in advancing our understanding of glioma etiopathogenesis [87]. Each omics layer provides unique insights into cellular functions, helping to unravel disease mechanisms, identify driver mutations, and stratify patients based on molecular profiles. However, these approaches often fail to capture tumor heterogeneity, spatial organization, and cell-cell interactions, limiting the ability to assess dynamic processes within the tumor microenvironment [88].

In recent years, single-cell transcriptomics (scRNA-seq) has revolutionized cancer research, including glioma biology, by

providing unprecedented resolution and depth [89]. This technology enabled the identification of multiple transcriptomic subtypes within individual tumors, detection of metastatic subpopulations, and discovery of predictive biomarkers, thereby facilitating drug response assessment and guiding treatment strategies [90]. Alongside scRNA-seq, spatial transcriptomics has emerged as a powerful tool for mapping the distribution patterns of gene expression and cellular interactions within the tumor microenvironment [91, 92]. Together, these methods allow the identification of spatially distinct cellular subpopulations, niche-specific gene expression signatures, and localized signaling pathways, offering a comprehensive view of tumor architecture and its interactions with neighboring cells and extracellular matrix [14, 93].

Although still in its early stages, the integration of single-cell and spatial transcriptomics is gaining momentum [92]. A recent integrated analysis of 201,986 human glioma cells revealed extensive intra- and inter-tumoral heterogeneity in immune cell composition across tumor regions and patients [88]. Both GBM and *IDH1*-mutant gliomas exhibited pronounced variability, reflecting diverse immune landscapes within spatially distinct regions [94].

In GBM, Ravi et al. identified five spatially distinct transcriptional programs: radial-glia, reactive-immune, neural development, spatial oligodendrocyte precursor cell and reactive-hypoxia, each associated with unique genomic alterations and shared transcriptomic signatures [95]. For example, the radial glia program is characterized by high expression of radial-glia-associated genes, such as *HOPX* and *PTPRZ1*, and astrocyte-related genes (*GFAP*, *AQP4*, *VIM*, and *CD44*). The reactive-immune program shows enrichment in inflammation-associated genes (*HLA-DRA*, *C3*, *CCL4*, and *CCL3*) and features interferon- γ signaling. The neural development and oligodendrocyte precursor programs align with neuronal and oligodendrocyte lineages, respectively. The reactive-hypoxia program involves hypoxia-response genes (*VEGFR*, *HMOX1*, *GAPDH*) and glycolytic genes (*LDHA* and *PGK1*) [95].

Similarly, Ren et al. defined four gene expression patterns (invasive, hypoxic, vascular and tumor core), with corresponding niche-specific markers [96].

Spatial transcriptomics has also facilitated the identification of therapeutic targets enriched in specific tumor regions, including *TP53*, *EGFR*, *FERMT1*, *CD44*, *S100A4*, and *SOX2*, particularly in blood vessel-rich and tumor-dense areas of high-grade gliomas (*IDH* wild-type and mutant) [97]. Yixin Fu et al. demonstrated distinct metabolic profiles across tumor regions: hypoxic cores rely on glycolysis and lactate metabolism (Warburg effect), whereas peripheral regions preferentially utilize glutamine metabolism and fatty acid oxidation [98].

These advancements position spatial-omics as a crucial layer in integrative multi-omics approaches, complementing molecular, genomic, and transcriptomic data. Moreover, spatially resolved molecular information aligns with the evolving paradigm of network-preserving neurosurgery. By linking region-specific tumor heterogeneity with functional brain circuits, spatial omics can inform surgical planning, guiding resection strategies

to minimize disruption of critical networks while targeting the most aggressive tumor regions. As highlighted by Zhao J. et al. [99], multimodal intelligent neurological imaging combined with minimally invasive surgical techniques enables precise tumor targeting while protecting and remodeling functional brain networks [99, 100]. Integration of omics data, neurobiology, advanced imaging, surgical technology, and computational modeling represents a paradigm shift toward precision surgery, balancing tumor control with preservation of brain network integrity and optimizing patient prognosis.

7 | Conclusions

Gliomas remain a formidable challenge in neuro-oncology due to their infiltrative behavior, molecular heterogeneity, and therapeutic resistance [101]. Advances in molecular profiling have led to the identification of novel genetic markers and transcriptional signatures, refining glioma classification and enhancing clinical management [102].

The rapid evolution of multi-omics data integration, combined with AI-driven analytical methods, is increasingly contributing to accurate tumor classification, patient outcome prediction, and optimized treatment selection [103–106]. AI-enhanced algorithms now facilitate the integration of imaging modalities (X-rays, MRIs, CT scans) and histopathological data with multi-omics datasets, creating a more comprehensive diagnostic and prognostic framework.

Despite these advances, challenges remain. Technical variability, sample heterogeneity, and data interpretation complexities can affect the reliability and reproducibility of molecular findings [107]. These issues are particularly evident in gene expression studies, where differences in platforms, study design, sex-dependent expression, and the dynamic nature of gene regulation necessitate longitudinal studies and functional validation to establish causal relationships between molecular alterations and glioma pathogenesis.

Nevertheless, ongoing research continues to yield promising results, supporting further investment in multidisciplinary omics approaches. As these strategies advance toward clinical translation, they hold the potential to enhance precision medicine and deliver meaningful therapeutic benefits to glioma patients.

Author Contributions

Conceptualization: G.M., V.L.C., S.C.; Writing – original draft preparation: G.M., V.L.C.; Writing – review and editing: G.M., V.L.C., G.G., G.M.; Supervision: S.C.; Funding acquisition: S.C.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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