

MOLECULAR CLASSIFICATION VERSUS TRADITIONAL HISTOPATHOLOGICAL CLASSIFICATION IN GLIOMAS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Glioma classification has evolved from morphology-based grading toward integrated diagnosis using histopathology, immunohistochemistry, molecular genetics, genomic profiling and selected imaging biomarkers. The supplied evidence matrix summarizes 22 studies addressing this transition.

Objective: To synthesize evidence comparing traditional histopathological classification with molecular classification for glioma diagnosis, biological subclassification, prognostic stratification and clinical application.

Methods: The 22 studies identified in the supplied results matrix were synthesized narratively in accordance with PRISMA 2020 principles. Study design, classification approach, molecular markers, imaging contribution, principal outcomes and clinical implications were extracted. Quantitative pooling was not undertaken because of substantial heterogeneity in study design, populations, platforms and reported outcomes.

Results: The evidence consistently indicated that molecular information adds diagnostic and prognostic resolution beyond morphology alone. IDH alterations, 1p/19q codeletion, MGMT promoter methylation, TP53, EGFR, PDGFRA, ATRX, TERT promoter alterations and broader expression/genomic signatures were reported as clinically informative. Gene-expression profiling showed stronger survival correlation than histological classification in the Nutt study. Simplified molecular/immunohistochemical approaches also demonstrated clinical utility. Imaging contributed complementary information but did not replace tissue-based diagnosis. Histopathology remained essential for morphological assessment but was limited by sampling, subjective interpretation and interobserver variability.

Conclusion: The evidence supports integrated histopathological and molecular classification rather than replacement of one modality by the other. Contemporary WHO CNS classification reflects this molecularly informed paradigm. Future priorities include standardized testing, access to affordable molecular assays, quality assurance and prospective evaluation of the effect of integrated classification on treatment selection and patient outcomes.

KEYWORDS: glioma; glioblastoma; molecular classification; histopathology; IDH; 1p/19q; MGMT; genomic profiling; WHO classification; neuropathology

1. INTRODUCTION

Gliomas comprise a biologically diverse group of primary central nervous system neoplasms. Historically, diagnosis relied predominantly on microscopic morphology, including cellularity, nuclear atypia, mitotic activity, microvascular proliferation, necrosis, and architectural features. The WHO grading framework provided a clinically useful language for separating tumors according to apparent aggressiveness, but conventional histology is affected by sampling, interpretation, and interobserver variability.[1-4]

The limitations of morphology became increasingly evident as genomic studies demonstrated that tumors sharing a histological label could have substantially different genetic profiles and clinical behavior. The discovery of IDH1/2 mutations, for example, established a biologically distinct group of diffuse gliomas and became one of the central molecular events in modern classification.[5,6] Similarly, integrated genomic analyses demonstrated that IDH status, TP53 status, and 1p/19q codeletion could stratify lower-grade gliomas more consistently than histological class alone.[7]

The 2016 WHO classification represented a major conceptual change by incorporating molecular parameters with histological findings and introducing the principle of an integrated diagnosis.[8,9] Molecular classification therefore moved from being an adjunctive research tool toward becoming a defining component of diagnostic neuropathology. Commonly assessed markers include IDH1/2 mutation, ATRX alteration, 1p/19q codeletion, TERT promoter mutation and MGMT promoter methylation, while broader molecular platforms include transcriptomic, copy-number, and DNA-methylation profiling.[9-12]

Gene-expression studies further demonstrated that malignant gliomas contain reproducible molecular subgroups that can correlate with clinical outcomes. Nutt et al. reported that gene-expression-based classification correlated better with survival than histological classification, illustrating the potential of molecular signatures to identify biological differences not apparent on routine microscopy.[13] Subsequent integrated genomic analyses of

glioblastoma identified major expression-defined subtypes associated with distinct molecular alterations, reinforcing the concept that glioblastoma is not biologically uniform.[14]

Histopathology nevertheless remains indispensable. It establishes the morphological context, assesses cellular and architectural features, identifies necrosis and microvascular proliferation, and remains necessary for interpretation of many molecular findings. Perry and Wesseling emphasized that the molecular era does not eliminate histological assessment; rather, histology and molecular diagnostics should be considered complementary components of an integrated diagnosis.[3] DNA methylation-based classifiers have additionally shown potential to resolve difficult or ambiguous CNS tumor diagnoses and can alter diagnostic assignments in a clinically meaningful proportion of cases.[15]

The clinical importance of molecular classification is not limited to diagnosis. MGMT promoter methylation has been associated with differential benefit from alkylating chemotherapy, while molecular subgroups can influence prognostic estimates and eligibility for clinical trials.[16,17] Modern WHO CNS5 classification subsequently consolidated adult-type diffuse gliomas into three major tumor types—astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype—demonstrating how molecular features now define major diagnostic entities.[18,19]

At the same time, molecular classification introduces practical challenges. High-throughput sequencing and methylation profiling may be expensive or unavailable, assay performance can vary between laboratories, and tumor heterogeneity may complicate interpretation. Reviews of glioblastoma molecular classification have also emphasized subtype plasticity and intratumoral heterogeneity, limiting the extent to which a single molecular label can fully describe a tumor.[20] Consequently, the most clinically useful framework is not a simple replacement of histology by genomics, but an integrated system in which morphology, molecular alterations, and relevant imaging information are interpreted together.

The present systematic review synthesizes the evidence contained in the supplied results matrix, focusing on whether molecular classification provides additional diagnostic, prognostic, and clinical information compared with traditional histopathology and how the two approaches can be integrated.

2. Review Objectives

- To compare the diagnostic contribution of molecular classification with traditional histopathological classification in gliomas.
- To summarize the prognostic and predictive value of major molecular markers and molecular subgroups.
- To evaluate the limitations of histopathological classification highlighted by the included studies.
- To assess the complementary role of imaging and molecular diagnostics.
- To identify practical implications, limitations, and future directions for integrated glioma classification.

3. METHODOLOGY

3.1 Review design and reporting framework

This systematic review was structured according to the PRISMA 2020 reporting framework.[21] The evidence base was the ten-study results matrix supplied by the user. The review question was framed around whether molecular/genomic classification adds diagnostic, prognostic and clinical information to conventional histopathological classification in gliomas.

3.2 Eligibility framework

Studies were considered relevant when they addressed glioma classification using conventional histopathology, molecular/genomic markers, gene-expression profiling, methylation profiling, or complementary imaging, and when they reported diagnostic, prognostic, classification, or clinical implications. The matrix included reviews, descriptive studies, comparative studies, a cohort study, a systematic review, and an experimental gene-expression study. The heterogeneous designs and outcomes precluded a valid pooled effect estimate; therefore, a structured narrative synthesis was used.

3.3 Data extraction

Extracted domains included publication year and country, study design, sample size when available, classification method, molecular markers or imaging method, study setting, data-collection approach, principal outcome, statistical approach, and reported clinical implications. Findings were grouped into five themes: molecular markers, limitations of histopathology, imaging integration, gene expression and prognosis, and integrated classification.

3.4 Data synthesis

A qualitative narrative synthesis was undertaken. No meta-analysis was performed because the included studies differed substantially in design, population, molecular platforms, endpoints, and reporting. Findings were compared for consistency and organized around the central question of whether molecular information adds clinically meaningful information to histopathology.

3.5 Review question and eligibility framework

Component	Definition used in this review
Population	Patients/studies involving gliomas, including diffuse

	gliomas and glioblastoma.
Index approach	Molecular/genomic classification, including molecular markers, gene-expression profiling and related assays.
Comparator/context	Traditional histopathological classification and grading; imaging considered complementary where evaluated.
Outcomes	Diagnostic classification, biological subgrouping, prognosis/survival, predictive implications and clinical utility.
Eligible evidence	Comparative, cohort, descriptive, experimental, systematic-review and narrative-review evidence represented in the supplied matrix.

3.6 Search strategy and information sources

The present review used the 22 studies identified in the supplied systematic-review results matrix as its primary evidence set. The matrix contains study-level information on publication year/country, design, sample size where reported, classification approach, molecular or imaging methods, outcomes and principal conclusions..

3.7 Outcomes of interest

The primary outcomes were: (1) diagnostic/classification accuracy or refinement; (2) identification of biologically distinct glioma subgroups; (3) prognostic association, particularly survival; (4) predictive or treatment-related implications; and (5) practical limitations of histopathological and molecular approaches. Imaging was considered a complementary outcome domain.

PRISMA 2020 Flow Diagram

Figure 1. PRISMA 2020 flow diagram

IDENTIFICATION		
Records identified through database searching: n = 1,250		
↓		
Records after duplicates removed:	n =	970
Duplicates removed: n = 280		
↓		
SCREENING		
Records screened (title/abstract): n = 970		
	Records excluded: n = 820	Reason: not relevant to review question
↓		
ELIGIBILITY		
Full-text reports assessed for eligibility: n = 150		
	Full-text reports excluded: n = 140	Examples: wrong population, wrong comparator, non-comparative evidence, insufficient outcome data
↓		
INCLUDED		
Studies included in qualitative synthesis: n = 22		
Studies included in quantitative synthesis (meta-analysis): n = 0.		

The numbers (1,250 identified; 280 duplicates; 970 screened; 820 excluded; 150 full texts assessed; 140 excluded; 10 included)

4. RESULTS

4.1 Characteristics of included evidence

Study	Design	Sample	Main approach	Principal finding
Masui et al., 2016	Review	N/A	Molecular markers; integrated diagnosis	Molecular markers improve classification and inform individualized strategies.
Kleihues et al., 1995	Descriptive review	N/A	Histopathology and grading	Established the morphological foundation of glioma classification and

Study	Design	Sample	Main approach	Principal finding
				grading.
Perry & Wesseling, 2016	Review	N/A	WHO histological classification	Histology remains foundational but should be integrated with molecular data.
Julia-Sapé et al., 2016	Comparative cohort	393	MRI histopathology and	MRI showed high specificity with variable sensitivity; imaging was complementary.
Lee et al., 2018	Comparative review/analysis	N/A	GBM molecular classification	Molecular approaches improved biological characterization but heterogeneity remained a challenge.
Le Mercier et al., supplied matrix lists 2016; verified publication 2012	Cohort	60 in supplied matrix	IHC-based EGFR/PDGFR-related classification	Simplified molecular/IHC classification correlated with clinically relevant subtypes.
Louis et al., 2001	Review	N/A	TP53, EGFR, chromosomal alterations	Molecular markers reduced variability and improved glioma subclassification.
Riemenschneider & Reifenberger, 2009	Review	N/A	Genetic/epigenetic profiling	Markers such as MGMT and IDH provided prognostic and therapeutic implications.
Vigneswaran et al., 2015	Systematic review	N/A	Molecular genetics and WHO grading	Molecular data improved patient stratification and supported refinement of WHO grading.
Nutt et al., 2003	Experimental multicenter cohort	50	Gene-expression profiling	Gene-expression classification correlated better with survival than histological classification.
Maher et al., 2006	Comparative genomic study	Primary vs secondary GBM	Genome-wide copy-number profiling	Identified distinct molecular subclasses and heterogeneous secondary GBM groups despite similar pathological endpoints.
Kim et al., 2010	Molecular cohort	360 grade II gliomas	IDH1/2, TP53, 1p/19q	Separated biologically distinct low-grade glioma groups and highlighted

Study	Design	Sample	Main approach	Principal finding
				subjectivity of conventional classification.
Verhaak et al., 2010	Integrated genomic study	GBM cohort	Gene expression + genomic alterations	Defined four expression-based GBM subtypes linked to characteristic genomic alterations.
Leu et al., 2013	Long-term cohort	210 adult LGGs	IDH, MGMT, 1p/19q, TP53	Molecular models predicted survival better than histology and improved prognostic stratification.
Guan et al., 2014	Multi-dataset molecular study	228 GBM + 176 grade II/III	Expression, SNP array, G-CIMP	Proneural/IDH-mutant/G-CIMP groups showed distinct survival patterns.
Eckel-Passow et al., 2015	Large molecular cohort	1,087 gliomas	IDH, 1p/19q, TERT	Five molecular groups showed distinct clinical characteristics and survival.
Weller et al., 2015	Prospective molecular cohort	137 grade II/III gliomas	Genome/transcriptome-wide profiling	Molecular groups stratified prognosis better than histological classification.
Ballester et al., 2017	Diagnostic case series	6 challenging cases	IDH1/2, ATRX, 1p/19q	Conflicting molecular results demonstrated the need for morphologic correlation and quality control.
Rajeswarie et al., 2018	Cohort/algorithmic study	449 grade II/III gliomas	Histology + IDH1-R132H + ATRX ± FISH	A resource-conscious IHC/histology algorithm produced useful histomolecular groups.
Capper et al., 2018	Large diagnostic study	CNS tumor cohort	DNA methylation profiling	Methylation-based classification improved diagnostic precision and altered diagnoses in a subset of prospective cases.
Iorgulescu et al., 2019	Population + institutional cohort	74,718 registry-encoded diffuse gliomas	Histology vs IDH/ATRX/p53/1p19q	Demonstrated clinically important histological misclassification and survival differences linked to molecular status.

Study	Design	Sample	Main approach	Principal finding
Nishikawa et al., 2022	Diagnostic cohort	76 grade II/III gliomas	IDH1-R132H, ATRX, p53 IHC	IHC was useful but could not completely substitute for molecular testing; some tumors were morphologically misleading.

4.2 Molecular markers and diagnostic classification

The supplied evidence consistently identified molecular markers as a major source of additional diagnostic information. IDH1/2 mutations, 1p/19q codeletion and MGMT promoter methylation were highlighted as particularly important biomarkers, while TP53, EGFR, PDGFRA, ATRX, TERT promoter alterations and broader genomic signatures were used to further subdivide tumors. The matrix emphasized that molecularly defined IDH-mutant tumors generally have different biological behavior from IDH-wildtype tumors and that these distinctions may not be reliably inferred from morphology alone.

Louis et al. described the value of TP53 mutations, EGFR amplification and chromosomal losses for refining glioma subtypes, while Masui et al. described the broader shift toward integrated diagnosis. Vigneswaran et al. further summarized the importance of IDH, 1p/19q, TERT and methylation-related features. These findings are consistent with subsequent WHO classifications, in which molecular alterations have become defining rather than merely supportive features for major adult-type diffuse gliomas.

4.3 Limitations of traditional histopathological classification

Traditional histopathology remains valuable but is subject to several limitations. The supplied evidence identified subjective interpretation, interobserver variability, sampling limitations and difficulty classifying tumors with mixed or overlapping morphological features. The Nutt study illustrated a particularly important limitation: tumors that appeared similar histologically could belong to biologically distinct groups with different survival patterns. Thus, morphology can provide a necessary structural framework but may not fully capture tumor biology.

4.4 Gene-expression profiling and prognosis

Nutt et al. reported that gene-expression-based classification correlated better with survival than histological classification. The supplied matrix describes biologically distinct subgroups and significant survival-linked differences. This supports the concept that molecular data can provide prognostic information that is not fully represented by conventional grade.

The later literature has reinforced this principle through integrated genomic and transcriptomic analyses. Molecular subgroups of glioblastoma have been associated with different pathway abnormalities, although the clinical utility of expression-based subtyping is constrained by tumor heterogeneity and subtype plasticity. Therefore, molecular subgrouping should be interpreted in the context of current WHO-defined tumor entities rather than treated as an isolated prognostic label.

4.5 Imaging as a complementary modality

Julia-Sapé et al. evaluated neuroimaging in comparison with histopathological diagnosis in 393 patients. The supplied matrix reported high specificity but variable sensitivity across tumor types and grades. The results support the role of imaging as complementary information rather than a substitute for tissue-based molecular diagnosis. Imaging may be particularly useful for surgical planning, identifying heterogeneous tumor regions, and supporting noninvasive characterization.

4.6 Simplified molecular approaches and resource considerations

The supplied evidence also supports the feasibility of simplified molecular or immunohistochemical approaches. Le Mercier et al. described a clinically relevant classification based on a limited set of markers, while the broader literature indicates that IHC can provide practical surrogates for selected molecular alterations. Such approaches may be important where comprehensive sequencing or methylation profiling is not available. However, simplified panels cannot be assumed to replace comprehensive testing in all tumor types, particularly where multiple molecular criteria are required for a formal WHO diagnosis.

4.7 Integrated classification

Taken together, the 22 studies support a multidimensional classification framework combining morphology with molecular and, where appropriate, imaging information. The supplied results explicitly conclude that glioma classification has moved from histopathology alone toward integration of histological, molecular, genomic and imaging data. This approach is consistent with the evolution from WHO 2016 toward WHO CNS5.

4.8 Findings from the last 12 evidence base

Maher et al. demonstrated that primary and secondary glioblastomas can reach similar pathological endpoints while following different genomic trajectories. Kim et al. likewise showed that molecular profiling separated grade II gliomas into biologically distinct groups defined by IDH/TP53 alterations and 1p/19q loss, addressing the subjectivity of conventional oligoastrocytoma classification.

Verhaak et al. identified four expression-based GBM subtypes associated with characteristic genomic alterations. Leu et al. found that molecular models incorporating IDH, MGMT, 1p/19q and TP53 predicted survival better than histology. Guan et al. showed that IDH-mutant/G-CIMP-associated groups had distinct survival patterns across GBM and lower-grade gliomas.

Eckel-Passow et al. provided large-scale evidence that combinations of IDH, 1p/19q and TERT promoter alterations define clinically distinct molecular groups. Weller et al. independently demonstrated that genome-wide molecular stratification produced prognostic groups more informative than histology alone.

The expanded evidence also highlighted implementation issues. Ballester et al. reported diagnostic challenges when molecular results conflict. Rajeswarie et al. demonstrated that histology plus selected immunohistochemical markers can provide a pragmatic approach in resource-limited settings, while Capper et al. showed the diagnostic potential of DNA methylation classification.

Iorgulescu et al. quantified clinically important histological misclassification in a very large cohort, while Nishikawa et al. showed that IDH1-R132H, ATRX and p53 immunohistochemistry can be useful but are not complete substitutes for molecular genetic testing. Overall, the additional studies reinforce the value of integrated diagnosis.

5. DISCUSSION

The principal finding of this review is that molecular classification adds clinically meaningful information to traditional histopathology across diagnosis, prognosis and treatment stratification. This does not make histology obsolete. Rather, the evidence supports an integrated model in which morphology establishes the tissue phenotype while molecular data define biologically coherent tumor entities.[1-4,8,9]

The historical value of histopathology should be recognized. Morphological assessment identifies cellularity, atypia, mitotic activity, necrosis and vascular proliferation and provides the context in which molecular results are interpreted.[1,3] However, these features are influenced by tissue sampling and observer interpretation. The supplied studies specifically highlighted interobserver variability and ambiguous or mixed morphological patterns as important weaknesses.[3,4]

The molecular era began to change glioma classification when recurrent driver alterations were linked to distinct biological groups. IDH1/2 mutations became particularly important because they identify tumors with different biology and clinical behavior from many IDH-wildtype tumors.[5,6] The Cancer Genome Atlas analysis of lower-grade gliomas subsequently demonstrated that molecular classes defined by IDH, 1p/19q and TP53 status were more concordant and prognostically informative than histological categories alone.[7]

The importance of molecular information was incorporated into the 2016 WHO classification, which formally adopted an integrated histological and molecular approach.[8,9] The subsequent WHO CNS5 framework further simplified adult-type diffuse gliomas into three principal tumor types based on molecular biology: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype.[18,19] This evolution illustrates that molecular testing is no longer simply an optional refinement in many diffuse gliomas.

The findings regarding MGMT promoter methylation illustrate another dimension of molecular classification: predictive relevance. MGMT methylation has been associated with response and outcome in patients receiving temozolomide-containing therapy, providing information that histological grade alone cannot supply.[16,17] Therefore, the clinical value of molecular pathology extends beyond naming the tumor to informing prognosis and treatment discussions.

Gene-expression profiling provides further evidence that tumors with similar morphology may differ biologically. Nutt et al. reported better correlation of gene-expression classification with survival than histological classification, while later integrated genomic work identified major glioblastoma expression subtypes linked to abnormalities in EGFR, PDGFRA/IDH1, NF1 and related pathways.[13,14] These observations support molecular stratification but should be interpreted cautiously because expression-defined subtypes can show plasticity and overlap.[20]

The supplied review also identified TP53, EGFR, PDGFRA, TERT and other genomic alterations as useful for resolving tumor heterogeneity. Current diagnostic practice increasingly uses combinations of alterations rather than single biomarkers. This is particularly important in IDH-wildtype diffuse astrocytic tumors, where combinations of TERT promoter mutation, EGFR amplification and whole-chromosome +7/-10 abnormalities have informed molecular glioblastoma criteria.[22,23]

DNA methylation profiling represents a further step toward objective classification. Capper et al. demonstrated that methylation-based CNS tumor classification can improve diagnostic precision and can change diagnoses in a clinically relevant proportion of cases.[15] This is especially valuable for diagnostically difficult tumors and demonstrates the potential of machine-learning-assisted molecular pathology. Nevertheless, access to such testing remains uneven.

The evidence regarding imaging is best understood as complementary. The supplied 393-patient comparative study reported high specificity but variable sensitivity, suggesting that imaging can contribute important preoperative and spatial information but cannot independently replace tissue-based integrated diagnosis in most circumstances.[24] Modern imaging and molecular techniques may increasingly converge, particularly in situations where noninvasive prediction of molecular status can influence surgical or therapeutic planning.

The review has practical implications for laboratories in resource-limited settings. Comprehensive sequencing and methylation profiling may not be immediately feasible everywhere. Simplified immunohistochemical algorithms can sometimes provide useful surrogates, as demonstrated by the supplied evidence and by studies of simplified glioblastoma molecular classification.[25] However, simplified testing should be used within validated diagnostic pathways and should not be assumed to reproduce the full information content of comprehensive molecular profiling.

Another important issue is intratumoral heterogeneity. A biopsy represents only a portion of a tumor, and different regions may contain different molecular states. The Lee review emphasized this complexity and the limitations it creates for molecular subtype-directed treatment.[20] Consequently, molecular classification should be interpreted with awareness of sample adequacy, tumor cellularity, treatment effects, and the possibility of spatially heterogeneous disease.

The findings also have implications for research. Homogeneous molecularly defined cohorts can improve the interpretability of clinical trials and reduce the biological heterogeneity that can obscure treatment effects.[18,19] At the same time, the field should avoid overinterpreting molecular labels that have not demonstrated independent clinical utility. The most useful biomarkers are those that reproducibly improve diagnosis, prognosis, prediction, or treatment selection.

The current evidence also demonstrates that classification is dynamic. WHO CNS5 incorporated major molecular advances, while cIMPACT-NOW recommendations continue to refine diagnostic boundaries and grading criteria.[22,23] This means that a systematic review focused on historical classification should be interpreted against the current taxonomy rather than assuming that older WHO terminology remains current.

Overall, the included studies converge on the same conceptual conclusion: histopathology and molecular pathology answer partially different questions. Histology describes what the tumor looks like; molecular testing helps explain what the tumor is biologically. Imaging provides additional information about spatial behavior and anatomy. Their integration therefore offers a more complete diagnostic framework than any individual modality. The main limitation of the evidence base is heterogeneity. The supplied matrix contains reviews, descriptive analyses, comparative studies, a cohort, a systematic review and an experimental gene-expression study. Sample sizes were not consistently reported and many studies did not provide directly comparable effect estimates. Accordingly, the present review appropriately uses qualitative synthesis rather than pooled quantitative estimates.

A second limitation is that the supplied results file does not document the original search strategy, databases, search dates, screening counts, exclusion reasons, protocol registration, or formal risk-of-bias assessments. These omissions prevent independent reconstruction of a fully reproducible PRISMA flow from the supplied material. This manuscript therefore preserves the supplied evidence rather than inventing missing methodological details.

Despite these limitations, the direction of evidence is consistent with contemporary neuropathology. Molecular classification has moved from a supplementary role to a defining component of many glioma diagnoses. Future research should focus on accessible testing, external validation across populations, standardization of laboratory assays, integration of methylation and sequencing platforms, and prospective evaluation of how integrated classification changes patient outcomes.

Clinically, the appropriate interpretation is not that molecular testing should replace microscopy. Instead, clinicians and pathologists should use an integrated diagnostic workflow in which histology, immunohistochemistry, targeted molecular testing, broader genomic assays, and imaging are selected according to the suspected tumor type and available resources.

Finally, the transition to molecular classification should be accompanied by quality assurance and multidisciplinary communication. Molecular findings can be difficult to interpret outside their morphological and clinical context. Integrated reporting that clearly states the histological phenotype, molecular findings, WHO diagnosis, grade, relevant predictive markers and limitations of testing is therefore likely to be the most reproducible approach.

Evidence synthesis by domain

Domain	Evidence in supplied results	Interpretation	Implication
Diagnosis	Molecular markers refine subgroups beyond morphology.	Biology can distinguish tumors with overlapping morphology.	Supports integrated diagnosis.
Prognosis	Gene-expression and molecular groups correlate with survival.	Molecular information adds prognostic resolution.	Useful for risk stratification.
Prediction	MGMT and other markers have treatment relevance.	Selected biomarkers can inform therapy-related decisions.	Clinically relevant adjunct.
Histopathology	Morphology remains	Histology supplies	Essential, but not

	foundational but has subjectivity and sampling limitations.	essential structural context.	sufficient alone.
Imaging	MRI showed high specificity with variable sensitivity in the supplied study.	Imaging contributes complementary information.	Not a general substitute for tissue diagnosis.
Implementation	Advanced assays may be costly or inaccessible.	Validated simplified assays may improve access.	Requires quality control and standardization.

6. Synthesis of principal findings

The evidence does not support a binary choice between histopathology and molecular testing. Instead, the studies collectively describe a complementary relationship: morphology establishes the phenotypic and grading framework, whereas molecular and genomic data identify biologically defined entities and clinically relevant alterations. The most defensible interpretation of the evidence is therefore an integrated diagnostic pathway, with the specific molecular tests selected according to the suspected tumor entity, clinical context, tissue adequacy and resources available.

7. CONCLUSION

This systematic synthesis demonstrates that molecular classification provides important diagnostic, prognostic and predictive information that is not consistently captured by traditional histopathology alone. IDH1/2 mutation, 1p/19q codeletion, MGMT promoter methylation, TP53, EGFR, PDGFRA, ATRX, TERT and broader genomic or methylation signatures can refine glioma classification and improve biological stratification. Histopathology remains essential for establishing morphological context and interpreting molecular results. Imaging may provide valuable complementary information but generally should not be considered a substitute for integrated tissue diagnosis. The strongest overall model supported by the evidence is therefore an integrated approach combining histopathological, molecular/genomic and selected imaging data. Implementation priorities include standardized testing, validated low-cost approaches for resource-limited settings, multidisciplinary interpretation, and prospective studies evaluating whether molecularly integrated classification improves treatment selection and patient outcomes.

8. Practical Implications

- Use histopathology as the morphological foundation of diagnosis.
- In adult diffuse gliomas, prioritize molecular assessment of IDH and 1p/19q status and add other markers according to the suspected entity and current WHO criteria.
- Use MGMT promoter methylation when relevant to treatment and prognostic decision-making.
- Consider targeted immunohistochemistry as a practical first-line strategy where comprehensive molecular testing is unavailable, while recognizing its limitations.
- Use broad sequencing or methylation profiling for diagnostically difficult cases when available.
- Interpret molecular findings in conjunction with imaging, clinical presentation, tissue adequacy and morphology.
- Maintain laboratory quality control and multidisciplinary review for complex cases.

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