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Artificial Intelligence in Neuro-Oncology: A Review of Radiomics and Machine Learning for Predicting Glioma Molecular Profiles

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ABSTRACT

Modern glioma diagnosis depends on molecular alterations that cannot be determined reliably from conventional imaging alone. Radiomics and machine learning attempt to bridge this gap by transforming magnetic resonance images into quantitative signatures associated with isocitrate dehydrogenase mutation, 1p/19q codeletion, O6-methylguanine-DNA methyltransferase promoter methylation, ATRX loss, and other clinically relevant profiles. This narrative review summarizes the principal workflows, reported performance, methodological limitations, and translational priorities of artificial intelligence in glioma radiogenomics. Evidence is strongest for noninvasive prediction of isocitrate dehydrogenase status, while results for 1p/19q and O6-methylguanine-DNA methyltransferase are promising but less stable across institutions. Handcrafted radiomics offers interpretability and modest data requirements, whereas deep learning can learn hierarchical spatial patterns but is more vulnerable to hidden confounding, scanner variation, and overfitting. Clinical adoption will require harmonized imaging, reproducible segmentation, transparent reporting, prospective multicenter validation, calibration analysis, and workflows that preserve tissue-based diagnosis as the reference standard. Artificial intelligence is therefore best viewed as a preoperative decision support and sampling tool rather than a replacement for neuropathology.

KEYWORDS:
artificial intelligence; glioma; radiomics; radiogenomics; machine learning; magnetic resonance imaging; molecular biomarkers

1. INTRODUCTION

Diffuse gliomas are no longer classified by morphology alone. The fifth edition of the World Health Organization classification integrates histologic findings with molecular alterations, particularly isocitrate dehydrogenase (IDH) status and chromosome 1p/19q codeletion, to define adult type diffuse gliomas (Louis et al., 2021; WHO Classification of Tumours Editorial Board, 2021). This shift improves diagnostic precision, yet it also exposes a practical problem. Definitive molecular characterization usually depends on tissue obtained through biopsy or resection, while treatment planning often begins before a complete molecular report is available.

Magnetic resonance imaging (MRI) contains information beyond visible anatomy. Tumor intensity, shape, texture, diffusion, perfusion, and spatial relationships may reflect cellularity, angiogenesis, necrosis, and microenvironmental heterogeneity. Radiomics converts these patterns into numerical features, while radiogenomics links imaging phenotypes to genomic or epigenomic states (Lambin et al., 2017; Singh et al., 2021). Machine learning can then combine imaging and clinical variables to estimate a molecular profile before surgery.

The clinical attraction is clear, but reported performance must be interpreted cautiously. Many studies are retrospective, single center, and based on public datasets with incomplete control of acquisition differences. High internal accuracy may fall when a model encounters a new scanner, institution, patient population, or segmentation protocol (Kawaguchi et al., 2021; Nayak et al., 2024). This review examines what current methods can predict, why results vary, and what is still required before an imaging based virtual biopsy becomes dependable.

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2. FROM MRI TO A MOLECULAR PREDICTION

A conventional radiomics pipeline begins with MRI acquisition and preprocessing, followed by tumor segmentation, feature extraction, feature reduction, model training, and validation. Common sequences include T1 weighted, contrast enhanced T1 weighted, T2 weighted, and fluid attenuated inversion recovery imaging. Diffusion and perfusion may add biologic information, although their availability and protocol variability can limit generalizability. Intensity normalization, resampling, registration, and bias field correction are important because many texture features are sensitive to voxel size and signal distribution.

Handcrafted radiomics typically measures first order intensity statistics, shape, and texture matrices. PyRadiomics has improved computational accessibility, while the Image Biomarker Standardisation Initiative has provided reference definitions and benchmark values (van Griethuysen et al., 2017; Zwanenburg et al., 2020). Feature selection is essential because a small cohort can otherwise be overwhelmed by hundreds or thousands of correlated variables. Logistic regression, support vector machines, random forests, and gradient boosting remain common because they can perform well in limited datasets and allow partial inspection of feature importance.

Deep learning replaces part of this engineered pipeline with convolutional or transformer based networks that learn image representations directly. It may also combine segmentation and molecular classification in a single model. This reduces dependence on handcrafted descriptors, but it does not eliminate preprocessing bias. A network may exploit age, tumor location, acquisition artifacts, or dataset specific characteristics that correlate with the label without representing tumor biology. Saliency maps are useful for inspection, yet they do not prove biological validity.

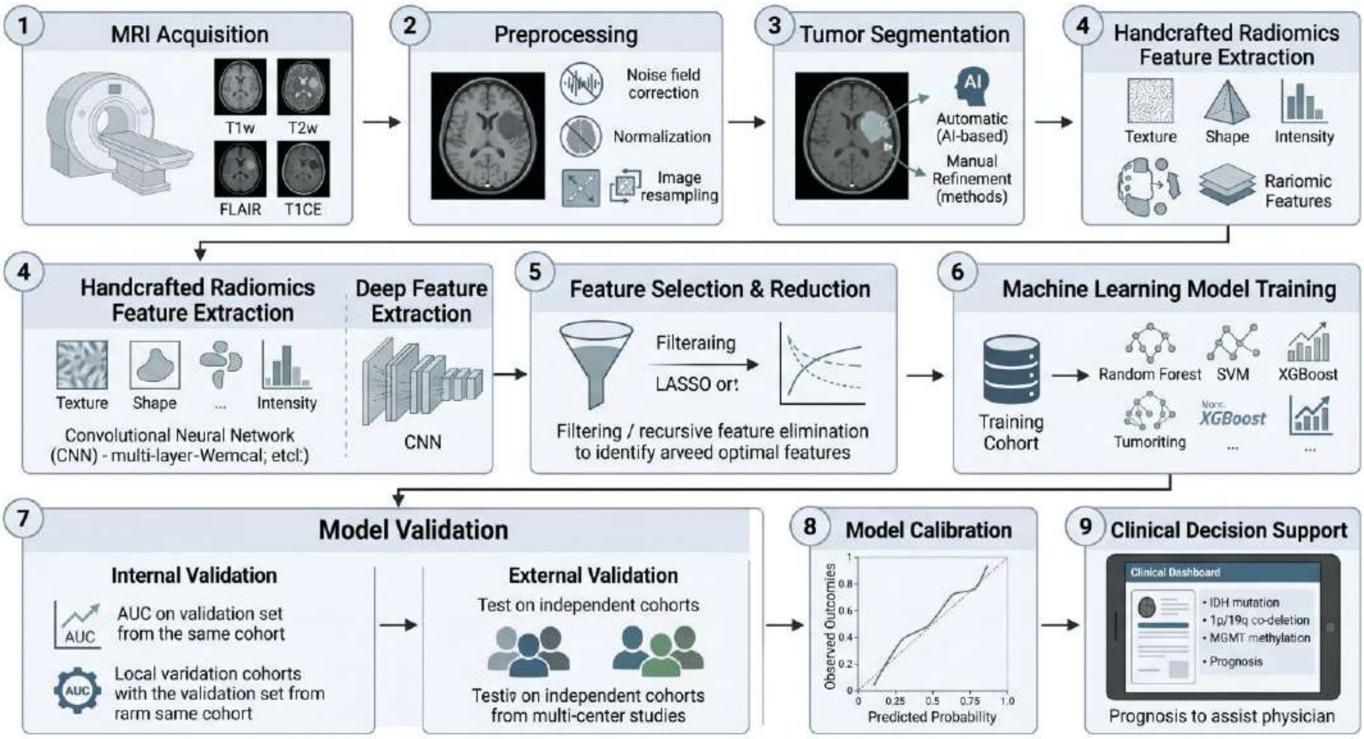

Figure 1. Proposed workflow for MRI based glioma molecular profiling. Suggested elements: MRI acquisition, preprocessing, tumor segmentation, handcrafted radiomics or deep feature extraction, feature selection, model training, internal validation, external validation, calibration, and clinical decision support.

3. PREDICTION OF MAJOR GLIOMA MOLECULAR PROFILES

3.1 IDH Mutation

IDH status is the most mature imaging target. IDH mutant gliomas often occur in younger patients and show imaging phenotypes that differ from IDH wildtype tumors, including location and growth pattern. Early radiomic studies showed that multiparametric MRI could stratify molecular and clinical phenotypes, and subsequent convolutional networks reported strong discrimination in multi institutional datasets (Kickingereder et al., 2016; Chang et al., 2018). A recent meta analysis of machine learning radiomics reported a pooled area under the curve of approximately 0.90, with sensitivity and specificity near 0.83 and 0.84, respectively (Chen et al., 2024). These results support real preoperative value, particularly when molecular testing is delayed or tissue sampling is constrained.

Even for IDH, performance is not uniform. Glioma grade, MRI sequence selection, inclusion of age and location, and validation design materially affect results. Models that include clinical variables may outperform image only systems because age and tumor site carry genuine diagnostic information. That benefit is clinically acceptable, but it should be described as multimodal prediction rather than pure image based inference.

3.2 1p/19q Codeletion

Complete 1p/19q codeletion is required for the diagnosis of oligodendroglioma in an IDH mutant diffuse glioma. Deep learning and texture based studies have reported useful discrimination from T2 and contrast enhanced MRI, including early convolutional approaches and later automated networks (Akkus et al., 2017; Kim et al., 2019; Yogananda et al., 2021a). Nevertheless, the target is more difficult than IDH because codeletion must be considered within the IDH mutant population, class sizes are often unbalanced, and histologic or molecular labels may come from different testing platforms. A staged model that first predicts IDH and then evaluates 1p/19q may better reflect the diagnostic hierarchy, although error can accumulate across stages.

3.3 MGMT Promoter Methylation

MGMT promoter methylation is clinically relevant because it is associated with greater benefit from alkylating chemotherapy in glioblastoma. MRI based radiomics and deep learning studies have reported high internal performance, including a T2 weighted network that combined tumor segmentation and methylation prediction (Yogananda et al., 2021b). However, systematic evaluations show substantial heterogeneity related to assay method, methylation threshold, tumor definition, image sequence, and validation strategy (Chen et al., 2022; Leone et al., 2025). MGMT prediction is therefore promising as a supportive estimate, but current evidence does not justify replacing laboratory testing.

3.4 Additional Markers and Integrated Classification

Research has expanded toward ATRX, TERT promoter mutation, EGFR amplification, CDKN2A/B deletion, and combined molecular classes. These targets may benefit from multitask learning because several alterations are biologically and diagnostically related. Integrated models can also predict the final WHO category rather than a single marker. The appeal is high, but the label space becomes more complex and some classes remain rare. Multicenter datasets with standardized molecular ground truth are therefore more important than increasingly elaborate architectures.

Table 1. Clinical interpretation of commonly predicted glioma molecular profiles

Target	Clinical relevance	Current AI evidence	Main limitation
IDH mutation	Defines major adult diffuse glioma groups and informs prognosis	Most consistent radiomic and deep learning performance	Dataset shift and dependence on grade, age, and location
1p/19q codeletion	Required for oligodendroglioma diagnosis in IDH mutant tumors	Promising, especially with multiparametric MRI	Smaller cohorts, class imbalance, hierarchical labeling
MGMT promoter methylation	Predicts benefit from alkylating therapy in glioblastoma	Variable but potentially useful as supportive evidence	Assay heterogeneity and weak external reproducibility
ATRX, TERT, EGFR, CDKN2A/B	Refines classification, prognosis, and biologic interpretation	Early evidence and growing multitask approaches	Rare labels, incomplete testing, limited multicenter validation

4. MODEL EVALUATION AND REPRODUCIBILITY

Model evaluation should extend beyond accuracy. Discrimination should be reported with confidence intervals, while calibration should show whether predicted probabilities correspond to observed risk. Sensitivity, specificity, positive predictive value, and negative predictive value depend on prevalence and may change across clinical settings. Decision curve analysis can estimate whether a model adds net benefit at plausible thresholds. External validation must use patients from a genuinely independent institution or time period, not a random subdivision of the same dataset.

Reproducibility is weakened by manual segmentation, inconsistent MRI preprocessing, feature instability, and information leakage. Segmentation remains a major source of variance, although automated methods developed through initiatives such as the Brain Tumor Segmentation challenge have reduced labor and improved consistency (Menze et al., 2015; Bakas et al., 2017). Feature selection, normalization, and augmentation must be performed within each training fold. If they are conducted before the data split, test information can leak into model development and inflate performance.

Reporting frameworks provide a practical safeguard. CLAIM emphasizes transparent description of datasets, reference standards, model design, evaluation, and failure analysis, while TRIPOD and PROBAST address prediction model reporting and risk of bias (Collins et al., 2015; Mongan et al., 2020; Wolff et al., 2019). The 2024 CLAIM update further reflects the need for clearer documentation of fairness, generalizability, and clinical context (Tejani et al., 2024).

Table 2. Minimum requirements for a clinically credible glioma radiogenomics study

Domain	Minimum expectation	Reason
Cohort	Consecutive or clearly sampled patients with explicit inclusion criteria	Reduces spectrum and selection bias
Reference standard	Validated molecular testing with assay and threshold reported	Prevents ambiguous or inconsistent labels
Imaging	Sequence parameters, preprocessing, harmonization, and missing data described	Allows replication and assessment of scanner effects
Segmentation	Method, annotator experience, and reproducibility analysis reported	Quantifies a major source of feature variability
Validation	Independent external cohort with calibration and confidence intervals	Tests transportability rather than memorization
Transparency	Code, model details, and preferably deidentified data or test set access	Supports verification and safe reuse

5. CLINICAL TRANSLATION AND FUTURE DIRECTIONS

The most realistic near term role is decision support before surgery. A calibrated model could suggest the probability of an IDH mutant tumor, support operative planning, prioritize molecular tests, or identify regions for targeted biopsy. It may also help when tissue is scant, risky to obtain, or potentially unrepresentative of a heterogeneous lesion. The model output should be presented with uncertainty and integrated with age, symptoms, tumor location, and conventional radiologic interpretation.

Several developments may improve translation. First, federated learning can permit multicenter training without centralizing identifiable images. Second, harmonization methods can reduce scanner and protocol effects, although they must be validated without erasing biological signal. Third, multitask models may jointly segment tumors and predict several molecular endpoints. Fourth, prospective silent deployment can reveal calibration drift and workflow problems before predictions influence care. Finally, uncertainty estimation and selective prediction can allow a model to abstain when a case falls outside its training distribution.

Clinical utility will depend less on a small gain in area under the curve than on trustworthy behavior in difficult cases. Models should be tested across institutions, demographic groups, tumor grades, and acquisition protocols. They should also be compared with neuroradiologists and with simple clinical baselines. A complex network that does not outperform age, location, and a few semantic MRI features may have limited practical value.[1]

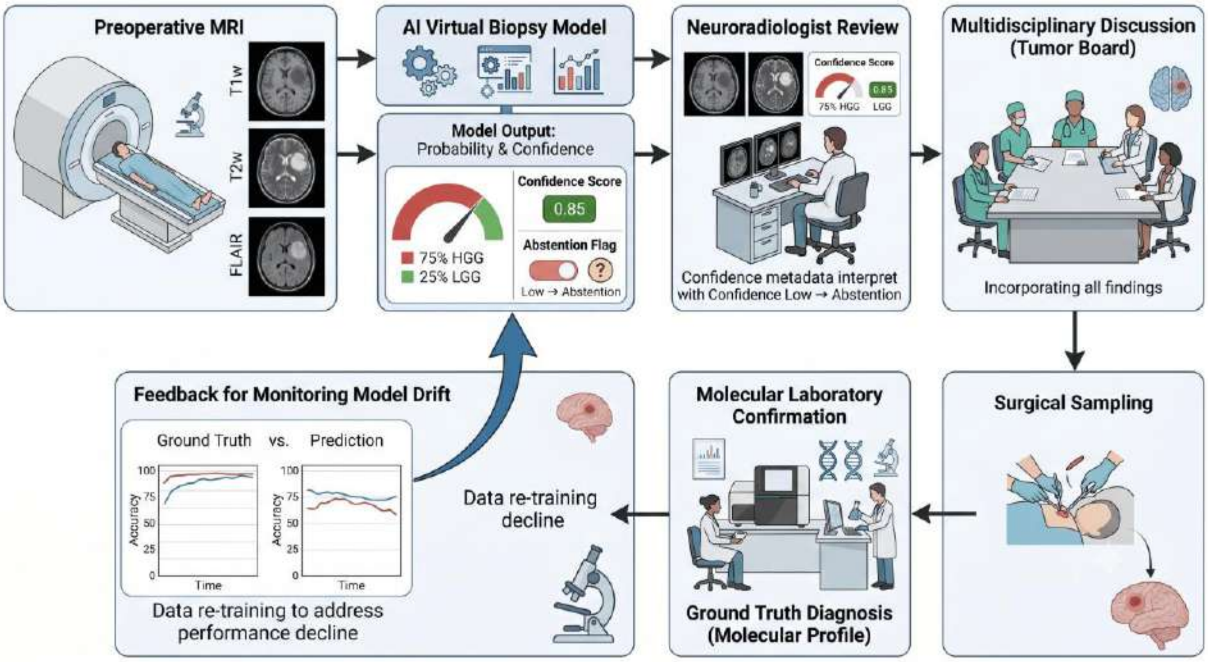

Figure 2. Suggested clinical integration of an AI based virtual biopsy. Suggested elements: preoperative MRI, model probability with confidence or abstention flag, neuroradiologist review, multidisciplinary discussion, surgical sampling, molecular laboratory confirmation, and feedback for monitoring model drift.

6. CONCLUSION

Radiomics and machine learning can extract molecularly relevant information from routine glioma MRI, with the strongest evidence currently supporting IDH prediction. Models for 1p/19q codeletion, MGMT promoter methylation, and additional alterations remain promising but show greater variability across cohorts and methods. The field is moving from proof of concept toward clinically oriented validation, yet tissue based molecular diagnosis remains indispensable. Progress will depend on reproducible preprocessing, standardized labels, external validation, calibrated probabilities, transparent reporting, and prospective evaluation within real neuro-oncology workflows. Used cautiously, artificial intelligence may become a valuable preoperative companion that guides sampling and decision making without overstating the certainty of an imaging derived molecular profile.

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