



Review

Artificial intelligence for brain cancer management: multimodal digital workflows for diagnosis, treatment planning, and longitudinal monitoring

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ABSTRACT

Brain cancers, especially glioblastoma, remain among the deadliest adult cancers, with outcomes largely unchanged despite multimodal treatments. This review summarizes cutting-edge artificial intelligence (AI) and machine learning (ML) advances transforming neuro-oncology in diagnostics, molecular profiling, treatment planning, and monitoring. Key findings show AI-driven radiomics and deep learning (DL) reaching over 90% accuracy in tumour segmentation and grading from MRI and whole-slide images, non-invasive *IDH/MGMT* prediction through liquid biopsy (LB) analysis, and augmented reality-guided resection that maximizes tumour removal while safeguarding expressive cortex. Treatment planning benefits from hybrid Convolutional Neural Networks (CNN)-Transformer models for immunotherapy stratification and blood-brain barrier penetrant drug repurposing, while real-time progression detection via multimodal integration helps differentiate true progression from pseudoprogression. Despite these advances, significant challenges remain, including data scarcity and imbalance in rare subtypes, domain shift due to imaging variability, black-box model behaviour eroding trust, regulatory requirements for prospective validation, and workflow fragmentation. Emerging solutions include federated and transfer learning for scalable model development, explainable AI (such as SHapley Additive exPlanations (SHAP) and attention interpretation for vision transformers) to foster clinician-AI collaboration, and foundation models pretrained on large-scale neuro-oncology datasets to facilitate personalization. Achieving this potential will depend on harmonized multi-omics registries, strong ethical and regulatory governance, and deliberate human-AI collaboration frameworks to integrate these tools into precision neuro-oncology.

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1. Introduction

Brain tumours comprise a heterogeneous group of primary and metastatic tumours that cause substantial morbidity, mortality, and socioeconomic burden, with gliomas representing the most common malignant primary brain tumours in adults. Glioblastoma (WHO grade 4 diffuse astrocytic glioma) is the most frequent and aggressive entity, characterized by rapid infiltrative growth, marked genomic heterogeneity, and almost uniformly fatal outcomes despite maximal multimodal therapy [1]. In modern practice, contemporary series report median overall survival of approximately 6–10 months in population-based cohorts and 12–21 months in clinical trial populations treated with resection, radiotherapy, and temozolomide, underscoring the persistently poor prognosis and limited curative benefit [2–4]. Unmet needs span the entire disease course. Diagnostic pathways are often suboptimal, with many glioblastoma patients first diagnosed via emergency presentations, reflecting delayed recognition of non-specific neurological symptoms and limited early access to specialist assessment [2]. Conventional imaging and histopathology, while essential, frequently fail to capture the full extent of intra-tumoural heterogeneity, infiltrative margins, and dynamic molecular evolution under treatment, constraining accurate risk stratification and treatment planning [5]. Prognostic models still rely largely on coarse clinicopathological variables and a small biomarker panel (for example, *IDH* mutation and *MGMT* promoter methylation), which account for only part of the observed variability in survival and treatment response [4]. Disease monitoring remains challenging because it is difficult to distinguish true progression from treatment-related change on MRI, quantitative imaging and molecular readouts are incompletely integrated into routine care, and quality-of-life and neurocognitive outcomes are not assessed systematically [3]. In parallel, patients and caregivers frequently experience gaps in supportive care, rehabilitation, psychosocial support, and clinical-trial access, all of which contribute to suboptimal outcomes.

These limitations highlight the need for approaches that can synthesize complex multimodal information at scale and generate individualized, context-aware predictions to guide decision-making [5,6]. Advances in AI and ML, particularly DL, are beginning to address this

gap by enabling systematic integration of radiology, digital histopathology, genomics, transcriptomics, LB, electronic health records, and patient-reported outcomes [7] (Figs. 1 & 2A). Multimodal learning frameworks, including graph neural networks and transformer-based architectures, can jointly model the complementary information embedded in these modalities, uncover latent phenotypes, and identify biomarkers of treatment response and resistance that may not be discernible in any single data source [6] (Fig. 2B). In glioblastoma and other aggressive brain tumours, such models have potential to improve noninvasive molecular profiling, refine prognostic stratification, optimize surgical and radiotherapy planning, and enable more precise, adaptive monitoring of disease trajectories over time [2,3,5] (Fig. 2C).

Against this backdrop, the aim of this review is to synthesize current evidence on AI and ML-driven approaches for integrating multimodal data into aggressive primary brain tumours, with a particular focus on glioblastoma. Specifically, we (i) outline key unmet clinical needs in diagnosis, treatment planning, prognosis, and monitoring; (ii) summarize methodological advances in AI applied to imaging, pathology, LB, and other data streams; and (iii) critically appraise the translational impact, limitations, and future directions of these technologies for personalizing care and improving outcomes.

1.1. Search strategy and selection criteria

This narrative Review was informed by searches of PubMed, Web of Science, Scopus, IEEE Xplore, and selected preprint servers for English-language articles published between Jan, 2020, and May, 2026, with emphasis on primary studies from 2024 to 2026. Search terms included “glioblastoma”, “glioma”, “brain tumour”, “artificial intelligence”, “machine learning”, “deep learning”, “radiomics”, “digital pathology”, “liquid biopsy”, “multimodal”, “foundation model”, “federated learning”, “pseudoprogression”, “response assessment”, “wearables”, and “patient-reported outcomes”. Priority was given to peer-reviewed multicentre studies, externally validated models, clinically relevant datasets, consensus guidance, and papers reporting implementation, regulatory, or equity implications. Preprints were considered only when they covered rapidly evolving technical resources not yet represented in

Table 1
Critical AI applications and technology readiness levels in brain tumour management. TRL mapping follows a generic ML/clinical AI adaptation of the TRL scale (1–9), where TRL 1–3 = basic research/proof-of-concept, 4–5 = early translational / feasibility, 6–7 = clinical validation and limited deployment, 8–9 = routine, scaled clinical use. These levels are indicative and should be interpreted by specific clinical indication, intended use, and validation status.

AI application in brain cancer	Example tasks / use cases	Indicative TRL in 2024–2026 (clinical AI context)	Key limitations at this stage	References
MRI-based radiomics and DL for diagnosis and grading	Automated tumour segmentation, glioma vs metastasis classification, WHO grade prediction, IDH/MGMT status prediction from pre-operative MRI	TRL 6–7 (prospective and early multi-centre validation for some models; not yet routine standard of care)	Data heterogeneity across scanners and centres, limited external validation, risk of overfitting, need for robust calibration and workflow integration	[128]
Digital pathology / WSI models (CNN/ViT) for classification and biomarker prediction	Tumour subtype classification on H&E WSIs, prediction of IDH, 1p/19q, MGMT, and other markers, automated mitotic counts and cell density maps	TRL 5–6 (robust retrospective evidence; limited external and prospective validation)	Pre-analytical variability (staining, scanning), large data volume, lack of harmonised pipelines, regulatory uncertainty for primary diagnosis	[44]
LB + AI (cfDNA/ctDNA, EVs, CTCs) for glioblastoma detection and monitoring	Detection of glioblastoma vs controls, molecular profiling (IDH, TERT, MGMT), MRD monitoring and progression vs pseudo-progression classification from cfDNA, EV RNA, proteomics	TRL 4–5 (promising single-centre and small multi-centre studies; early clinical feasibility)	Low analyte abundance, lack of standardised pre-analytics, small cohorts, confounding by clonal haematopoiesis, need for multi-centre prospective trials	[111]
Prognostic and treatment-response models from multimodal data	Survival prediction from MRI + clinical + molecular data; prediction of radiotherapy / chemo-response; risk stratification for trial enrolment	TRL 5–6 (multiple retrospective multi-centre studies; limited prospective deployment)	Dataset shift, inconsistent endpoints, lack of impact studies, unclear clinical thresholds for action	[64]
Intraoperative and AR-assisted surgical guidance	AI-enhanced neuronavigation, real-time 3D overlays of tumours and critical tracts, intraoperative MRI/ultrasound/SHG interpretation	TRL 6–7 (site-specific clinical deployment, early real-world experience)	Hardware integration, user-interface design, prospective evaluation of safety and benefit, cost and training requirements	[44]
Foundation and few-shot models for rare glioma subtypes	Zero-/few-shot classification of rare tumours, transfer learning from large generic imaging/genomics corpora (e.g. TCGA, UK Biobank)	TRL 3–4 (early research and proof-of-concept)	Limited task-specific validation, risk of hidden biases from pretraining data, unclear regulatory pathway	[129]
Physics-informed neural networks and mechanistic digital twins	Tumour growth modelling, virtual radiotherapy planning, prediction of spatiotemporal treatment effects at patient level	TRL 2–3 (early-stage research, largely preclinical / simulation studies)	Model identifiability, data requirements for personalisation, computational cost, lack of clinical validation	[101]

Table 2a

Clinical domain map for AI-derived multimodal biomarkers in neuro-oncology. Rows represent distinct translational domains spanning the continuum of brain tumour management. For each domain the table identifies the biomarker type produced (per FDA–NIH BEST taxonomy [130]), the evidentiary requirements for clinical use, the principal barriers encountered in brain cancer, and representative study examples. Abbreviations: cfDNA, cell-free DNA; ePRO, electronic patient-reported outcome; EV, extracellular vesicle; LGG, low-grade glioma; MRD, minimal residual disease; scRNA, single-cell RNA sequencing; snRNA, single-nucleus RNA sequencing.

Translational domain	Example multimodal inputs	Typical AI task	Biomarker type produced	What must be shown before clinical use	Main barriers in brain cancer	Representative application case(s) [Refs]
Integrated diagnosis	MRI radiomics + digital pathology + tissue genomics + LB	Classification, subtype prediction, latent-state discovery	Diagnostic biomarker	Concordance with reference diagnosis, external validation, robustness across scanners and platforms	Small cohorts, domain shift, incomplete matched datasets	MRI-based imaging-first models inferring molecular status and prognosis from baseline scans; multimodal pathology-imaging-genomics workflows for integrated classification [58,107]
Risk stratification	Baseline MRI + clinical variables + molecular markers + transcriptomics	Survival modelling, risk clustering	Prognostic biomarker	Calibration, reproducibility, incremental value beyond standard clinicopathological factors	Overfitting, cohort bias, inconsistent endpoints	GlioSurv integrated MRI, clinical/molecular variables, and treatment data for individualized survival prediction with external generalization; multimodal survival models after chemoradiotherapy [108,131]
Therapy selection	MRI habitats + MGMT/IDH/TERT status + immune signatures + treatment history	Response prediction, treatment benefit estimation	Predictive biomarker	Evidence of differential treatment benefit, not only outcome association	Confounding in observational datasets, limited prospective validation	MRI-based radiomics and multimodal models for temozolomide benefit and MGMT-linked response prediction; immune-response prediction using gene panels for checkpoint therapy [43,61]
Longitudinal monitoring	Serial MRI + LB + symptoms/ePROs + steroid exposure	Time-aware prediction, progression classification	Monitoring biomarker	Temporal stability, sensitivity to change, prospective assessment against clinical endpoints	Sparse follow-up, irregular sampling, pseudoprogression/radionecrosis overlap	Multiparametric MRI plus MGMT model evaluated with a random internal 20% test split; self-supervised multimodal model tested in an independent external cohort (n = 20); prospective single-centre serial MRI-habitat study (n = 79); and brain-tumour digital phenotyping/wearable feasibility studies (n = 15 and n = 54) [96,97,104,132,133]
Minimal residual disease / recurrence tracking	ctDNA/EVs + post-treatment MRI + clinical course	Residual disease detection, recurrence forecasting	Dynamic monitoring biomarker	Assay sensitivity at low tumour burden, reproducibility across serial time points, integration with imaging	Low analyte abundance, BBB effects, pre-analytical variability	Liquid-biopsy plus AI workflows for progression/recurrence monitoring and pseudoprogression discrimination using cfDNA, EV RNA, and proteomic readouts [22,28,111]
Tumour ecosystem stratification	sc/snRNA-derived states + spatial/pathology features + MRI phenotypes	Patient subgrouping, ecosystem inference	Biology-informed stratification biomarker	Biological plausibility, reproducibility across datasets, association with actionable outcomes	Incomplete spatial matching, batch effects, limited paired cohorts	Pediatric low-grade glioma study combining multiparametric MRI and RNA-seq to define immune clusters and therapy-resistance states; recurrence timing from integrated transcriptomic models [106,110,134]
Decision support at point of care	Any of the above, with uncertainty estimates and missing-modality handling	Multimodal fusion with interpretable outputs	Actionable composite biomarker	Transparent contribution of modalities, graceful degradation, workflow feasibility, clinical utility	Black-box behavior, missing data, real-time deployment constraints	Multimodal fusion systems designed for longitudinal support and integrated progression models combining imaging with clinical/radiotherapy variables [63,65,108]

Table 2b

Stage-based translational pipeline for AI-derived multimodal biomarkers in clinical neuro-oncology. Stages follow a generic TRL (Technology Readiness Level) adaptation for clinical AI, anchored to FDA–NIH BEST biomarker validation principles [130] and SaMD-related (Software as a Medical Device) regulatory considerations⁷¹ and TRIPOD + AI reporting guidance [112]. Performance thresholds are indicative; pre-specified decision criteria should be established prospectively per clinical indication and reported per TRIPOD + AI standards. Abbreviations: AUC, area under the receiver operating characteristic curve; C-index, concordance index; ComBat-seq/Harmony, batch-effect correction methods; DCA, decision curve analysis; FHIR, Fast Healthcare Interoperability Resources; MOFA +, Multi-Omics Factor Analysis; PRO, patient-reported outcome; SaMD, Software as a Medical Device; SHAP, SHapley Additive exPlanations; TRL, Technology Readiness Level; UMAP, Uniform Manifold Approximation and Projection; VAE, variational autoencoder; ViT, Vision Transformer.

Stage	Multimodal inputs	AI approach	Performance requirements	Neuro-oncology-specific challenges	Representative examples in glioblastoma / primary brain tumours
I Discovery & feature engineering (TRL 2–4)	Multiparametric MRI (T1, T2, FLAIR, DWI, perfusion) Digital pathology WSI (H&E, IHC) Bulk RNA-seq / DNA methylation arrays LB: ctDNA, EV cargo, protein panels Clinical / demographic variables	Unsupervised representation learning (autoencoders, VAEs, UMAP) Attention-based feature selection; SHAP-guided dimensionality reduction Self-supervised pretraining on unlabelled imaging/omics corpora Multi-omics factor analysis (MOFA+) for latent biomarker discovery	Internal cross-validation AUC / C-index reported with 95% CI Biologically plausible feature attribution (SHAP, attention maps) Calibration plot and Brier score on held-out split	Small annotated cohorts and severe class imbalance in rare subtypes Incomplete multimodal annotation (mismatched imaging–omics pairs) Selection bias in retrospective data; label heterogeneity across centres	Radiomic feature discovery from BraTS/TCGA corpora Self-supervised ViT pretraining on 2317 unlabelled glioma MRIs ¹²⁷ Transcriptomic immune cluster discovery in paediatric LGG [106]
II Analytical validation (TRL 4–5)	Same modalities as Stage I ≥ 2 external, geographically distinct cohorts with standardised acquisition Federated dataset access where raw data sharing is restricted	Locked model architecture with fixed preprocessing pipeline Uncertainty quantification (Bayesian DL, conformal prediction) Domain adaptation / federated learning for cross-site robustness Explainability: SHAP values, attention attribution reported per modality	External AUC / C-index replicated on ≥ 2 independent cohorts Calibration and DCA demonstrating net clinical benefit over current standard TRIPOD + AI-compliant reporting; feature reproducibility assessed	Domain shift from scanner variability and differing institutional protocols Batch-effect correction across multi-site omics (ComBat-seq, Harmony) Inconsistent endpoint definitions (RANO vs volumetric vs clinical progression)	GlioSurv: external C-index 0.61–0.80 across multimodal fusion configurations [108] Multi-task network externally validated across 2776 gliomas (C-index 0.67–0.72) [107] Pseudoprogression SVM: AUC 0.84 on independent test set [96]; self-supervised multimodal model: AUC 0.753 in an independent external cohort (n = 20) [97]
III Late external validation & prospective-ready evaluation (TRL 5–7)	Prospectively acquired multimodal data per pre-registered protocol Structured PRO / wearable streams alongside serial imaging Harmonised multi-omics registry with biobanked LB samples	Real-time inference pipeline integrated with clinical imaging workflow Federated / continual learning across trial sites Longitudinal updating of patient-specific risk scores as new data arrive	Non-inferiority or superiority to current standard decision pathway Net reclassification improvement; clinician decision concordance Pre-specified clinical action threshold; DCA benefit demonstrated prospectively	FDA SaMD classification and CE-marking requirements for AI-driven diagnostic tools ⁷¹ Ethical governance: informed consent for AI-assisted decisions; equitable access across demographics Prospective multi-site trial infrastructure and funding for rare-tumour subgroups	nnU-Net progression segmentation: Dice 0.79 (internal) / 0.73 (external); AUC 0.84 internally and 0.91 externally for recurrence versus post-treatment change [95]. Prospective serial MRI-habitat risk score: 12-month AUC 0.762 versus 0.646 for tumour volume (single centre, n = 79) [133]. Multimodal survival model: C-index 0.77 internally and 0.73/0.63 in two external cohorts, with time-dependent explanations [135]
IV Clinical integration & post-deployment monitoring (TRL 8–9)	Full EMR-integrated multimodal streams: serial imaging, LB, PROs, wearable signals FHIR / DICOM-structured interoperability across institutions	Edge-deployed models for real-time clinical decision support Continual learning with post-deployment drift detection and model versioning Human-AI collaborative interface with uncertainty communication	Real-world effectiveness: survival / QoL improvement demonstrated at population level Bias audit across demographic and institutional subgroups Audit trail and accountability framework established per regulator guidance	Model drift from biological and technical data-distribution shifts over time Liability and accountability in cases of AI-influenced erroneous decisions Health equity: ensuring performance is maintained for underrepresented patient groups	Population-level evidence on post-deployment effectiveness specific to brain tumours is still lacking.

peer-reviewed literature. Studies were selected based on relevance to multimodal AI workflows in neuro-oncology, with preference for those including external validation, prospective elements, or clear translational insights over single-centre retrospective reports.

cells and link histological architecture with molecular and clinical outcomes.

Vision Transformer (ViT)-based weakly supervised models on WSIs have achieved high performance in classifying primary brain tumour

Box 1: Glioblastoma is the most common and aggressive primary malignant brain tumour in adults (WHO grade 4 astrocytoma), arising from glial cells and exhibiting rapid proliferation, extensive necrosis, microvascular proliferation, and diffuse infiltration into surrounding brain tissue. Typically diagnosed in older age, glioblastoma presents with nonspecific symptoms including headaches, seizures, cognitive changes, personality alterations, nausea, and focal neurological deficits driven by mass effect and edema [1]. Key molecular hallmarks include *EGFR* amplification, *TERT* promoter mutations, chromosome 7 gain/10 loss, and frequent alterations in *RTK/Ras/PI3K*, *p53*, and *RB* pathways; ~35–40% show *MGMT* promoter hypermethylation predicting temozolomide response [2,5]. Despite maximal surgery, radiotherapy, and chemotherapy, median survival remains poor at approximately 6–10 months in population-based cohorts and 12–21 months in selected clinical trial populations with molecularly defined disease, with near-universal recurrence due to tumour heterogeneity and blood-brain barrier limitations. Advanced imaging reveals characteristic ring-enhancing lesions with central necrosis on contrast MRI [3].

2. AI in Brain Cancer Diagnostics

2.1. Radiomics and Imaging-Based Approaches

Radiomics transforms MRI, PET, CT and functional imaging into quantitative descriptions of tumour shape, intensity, texture, vascularity, diffusion restriction and spatial heterogeneity, which are not reliably captured by visual inspection alone. In brain tumours, these features support segmentation, grading, differential diagnosis, molecular-status inference and response assessment. Notably, their value depends strongly on standardisation: scanner vendor, field strength, acquisition parameters and preprocessing can shift feature distributions, making harmonisation and external validation essential [8].

A typical workflow comprises preprocessing, tumour or habitat segmentation, feature extraction, feature reduction and model training for classification, regression or survival tasks. Conventional statistical models and machine-learning methods, including deep networks that learn image representations directly, have been applied to glioblastoma grading, distinction from metastases, subtype classification and molecular marker prediction. While reported gains over expert assessment alone are encouraging, many studies remain vulnerable to overfitting, small or single-centre cohorts, inconsistent annotations and heterogeneous imaging protocols [8,9].

Translation therefore depends on treating radiomics as a regulated biomarker-development pipeline rather than a feature-discovery exercise. Analytical validation should test repeatability, robustness to pre-processing choices and domain shift; clinical validation should use independent, preferably multicentre cohorts with prespecified endpoints. Increasing model complexity also raises interpretability concerns, although saliency maps, SHapley Additive exPlanations (SHAP) and Attention Mechanisms can help expose which image regions or features drive predictions [10] (Table 1). Open-source platforms can lower implementation barriers, while transfer learning, few-shot learning and privacy-preserving federated learning may reduce the need for large centrally hosted datasets and allow multi-institutional training without raw image sharing [11].

2.2. Pathology and Digital Histology

Digital pathology uses whole-slide imaging of haematoxylin and eosin (H&E) stained sections to support AI-assisted brain tumour diagnosis. Applications include tumour classification, grading, molecular-marker inference (including *IDH* mutations status under the 2021 WHO CNS classification), cell quantification, and analysis of the tumour immune microenvironment [12]. The main advantage is scale: once slides are digitised, algorithms can examine patterns across millions of

types/subtypes and inferring diagnostic molecular markers (*IDH1* mutation AUC 0.960, *p53* mutation 0.874, *MGMT* methylation 0.845) directly from H&E images, with gradient-based attribution revealing interpretable histopathological features [13]. Hybrid 2D-3D CNN architectures can capture hierarchical spatial/contextual patterns for grading, outperforming prior methods (e.g., 97.1% accuracy/precision/specificity on TCGA; 95% on DeepHisto) [14].

Automated cell/nuclei detection addresses challenges like variable appearance and touching cells. Examples include Trainable Weka Segmentation workflows for quantifying brain metastases on murine WSIs (high correlation with manual assessment, $R^2=0.8783$) [15] and ensemble pipelines distinguishing gliomas from metastases post-MRI segmentation (ACC 0.895, AUC 0.9585) [16].

For non-invasive *IDH* mutation predictions, clustering-based hybrid CNN-ViT models on annotation-free H&E WSIs from 2275 diffuse glioma patients have achieved AUCs of 0.973 (validation) and 0.953 (external test), with strong performance across histologically similar subgroups (0.850–0.985) [17]. Complementary radiomics approaches predict *IDH* from preoperative non-contrast CT [18].

Tumour microenvironment analysis benefits from AI: multiplex imaging and RNA-seq studies reveal immune signatures (e.g., enriched M1 microglia, PD1+ cells in tumours) [19]. The GigaTIME multimodal framework has translated H&E to virtual multiplex immunofluorescence across large cohorts (e.g., 14,256 patients, 299,376 virtual slides spanning 24 cancer types), uncovering thousands of protein-biomarker-staging-survival associations validated on TCGA [20]. These pathology AI tools are being increasingly used to augment pathologist expertise, enabling faster, scalable, and precise diagnostics while complementing imaging-based approaches.

2.3. Liquid Biopsy and Biomarker Detection Methods

2.3.1. Liquid biopsy diagnostics

Liquid biopsy provides a minimally invasive approach for detecting and profiling brain tumours by analyzing tumour-derived components, such as circulating tumour DNA (ctDNA), circulating tumour cells (CTCs), extracellular vesicles (EVs), cell-free RNA (cfRNA), tumour-educated platelets (TEPs), proteins (e.g., NfL, GFAP, S100B), and metabolites in biofluids including blood, cerebrospinal fluid (CSF), urine, or saliva [21]. Combined with molecular techniques (qPCR, digital PCR, NGS) and AI, LB supports longitudinal monitoring of tumour heterogeneity, progression, treatment response, recurrence, and differentiation of true progression from pseudoprogression [22].

In brain tumours, LB sensitivity was constrained by the blood-brain barrier (BBB), low analyte abundance, and variable tumour shedding. Cerebrospinal fluid (CSF) usually offers higher sensitivity than plasma because of its proximity to the central nervous system, although blood-

based approaches are improving with ultrasensitive and targeted sequencing, methylation assays, extracellular-vesicle profiling, and integrated biosensor platforms [22].

Despite clear advantages, such as enabling repeatable sampling and preoperative “integrated diagnosis” for tumours in surgically inaccessible locations, clinical adoption remains limited by challenges including low and variable biomarker shedding (partly mitigated by emerging sonobiopsy via MR-guided focused ultrasound to transiently disrupt the BBB [23]), false positives from clonal hematopoiesis (prevalent in ~20% of glioblastoma cases and linked to poorer outcomes [24]), lack of standardized protocols for sample handling and analysis [25], and the complexity of high-dimensional, heterogeneous multi-omics datasets that exceed traditional statistical capabilities [26].

Integration of AI in LB analysis helps addressing the latest issues through batch-effect correction, missing-data imputation, normalisation, ontology mapping, and multimodal modelling [27]. Classical ML methods such as support vector machines, random forests, AdaBoost, and k-nearest neighbours remain useful for structured liquid-biopsy and omics data [28], whereas DL is better suited to high-dimensional or spatially organised inputs. However, performance claims should be

interpreted cautiously unless pre-analytical variation, low disease burden, and independent validation have been explicitly handled [29]. Interpretability methods, including pathway enrichment and feature-attribution analyses, should be used to connect predictions with plausible tumour biology rather than to justify opaque models after the fact.

Importantly, AI-enhanced LB should be framed as a valuable adjunct to imaging and tissue diagnosis, particularly for longitudinal monitoring and minimal residual disease detection, rather than as a near-term replacement for histopathological confirmation. It should be emphasized that biological and pre-analytical limitations (low analyte abundance, BBB constraints, clonal haematopoiesis, and variability in sample processing) cannot be fully overcome by AI alone. Its most realistic near-term role is to complement conventional approaches by enabling repeat sampling for treatment response, recurrence monitoring, and clarification of ambiguous imaging findings [36]. Future studies should prioritise standardised pre-analytics, longitudinal sampling with matched imaging, external multicentre validation, calibration assessments, and decision-curve analyses to demonstrate clinical utility (e.g., changes in biopsy strategy, follow-up intensity, or trial referral).

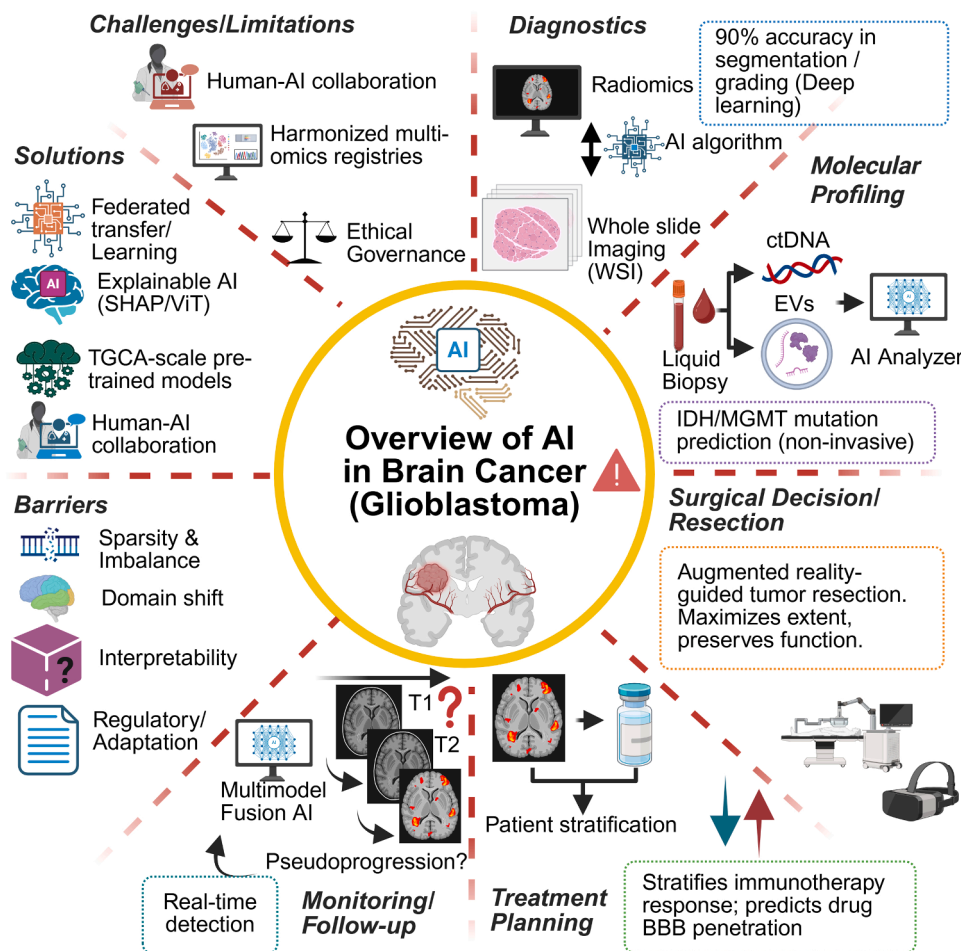


Fig. 1. AI-enabled workflow for brain cancer management. The central hub depicts AI as an integration layer connecting multimodal data streams to clinical decision points across diagnosis, molecular profiling, surgery, treatment planning, and follow-up. The diagnostics sector highlights radiomics and DL applied to structural and multiparametric MRI and whole-slide imaging for segmentation, grading, classification, and molecular-marker prediction in selected reference cohorts. Molecular profiling illustrates liquid-biopsy analysis of circulating tumour DNA and extracellular vesicles for non-invasive molecular inference and longitudinal tracking. Surgical decision-making includes augmented-reality guidance and intraoperative AI tools that aim to maximise safe resection while preserving function. Monitoring and treatment planning show multimodal fusion of serial MRI, pathology, molecular markers, and clinical variables to support progression assessment, pseudoprogression differentiation, risk-adapted follow-up, and trial selection. The barriers and solutions panels summarise data scarcity, domain shift, interpretability, federated learning, transfer learning, governance, and human-AI collaboration. This figure was generated using the BioRender software (www.biorender.com).

2.4. Statistical Foundations for AI-Driven Precision Oncology in Glioblastoma

MRI, digital pathology, genomics, and LB capture complementary dimensions of glioblastoma biology, including spatial heterogeneity, histology, and molecular alterations [30]. However, cohorts remain small and uneven, and scanner, staining, sequencing, and institutional effects can overwhelm weak biological signals. Statistical methodology has been therefore central to clinical-grade AI: it defines what can be estimated, how uncertainty is handled, and whether predictions improve decisions.

Modern pipelines combine ML with penalized regression, hierarchical/Bayesian modeling, ensembles, and survival frameworks. These approaches stabilize estimates, shrink noisy features, separate population-level effects from patient-specific variation, and support fusion of radiomic, molecular, and clinical covariates. In glioblastoma, AI models have targeted survival prediction and molecular-status inference, sometimes outperforming conventional models in development cohorts; nonetheless, recent systematic evidence highlights small samples, heterogeneous endpoints, limited external testing, and inconsistent reporting as persistent barriers [31].

Propensity-score methods, marginal structural models, and graphical

causal models may reduce bias due to measured confounding in radiomics and omics analyses, provided that their underlying assumptions are plausible; however, they cannot eliminate bias arising from unmeasured confounding, selection mechanisms, or model misspecification [32]. Evaluation should move beyond AUC or concordance indices to include calibration-in-the-large, calibration slope, overall prediction error, time-dependent performance, and decision-curve or net-benefit analyses. Decision thresholds should be clinically justified and linked to actionable consequences, such as changes in monitoring, LB or tissue biopsy (TB) strategy, trial referral, or therapy selection [33].

For multimodal AI, methodological rigour depends on appropriate regularisation, explicit reporting of missing-data and missing-modality patterns, and systematic assessment of dataset shift across institutions and protocols. Imputation, harmonisation, feature selection, and other data-driven pre-processing procedures should be conducted within each resampling or cross-validation fold to prevent information leakage and optimistic performance estimates. Nested cross-validation supports model tuning and internal validation but does not replace temporal, geographical, or independent multicentre validation. Transparent reporting should include preprocessing procedures, feature definitions, uncertainty estimates, code availability, and model performance when individual modalities are missing.

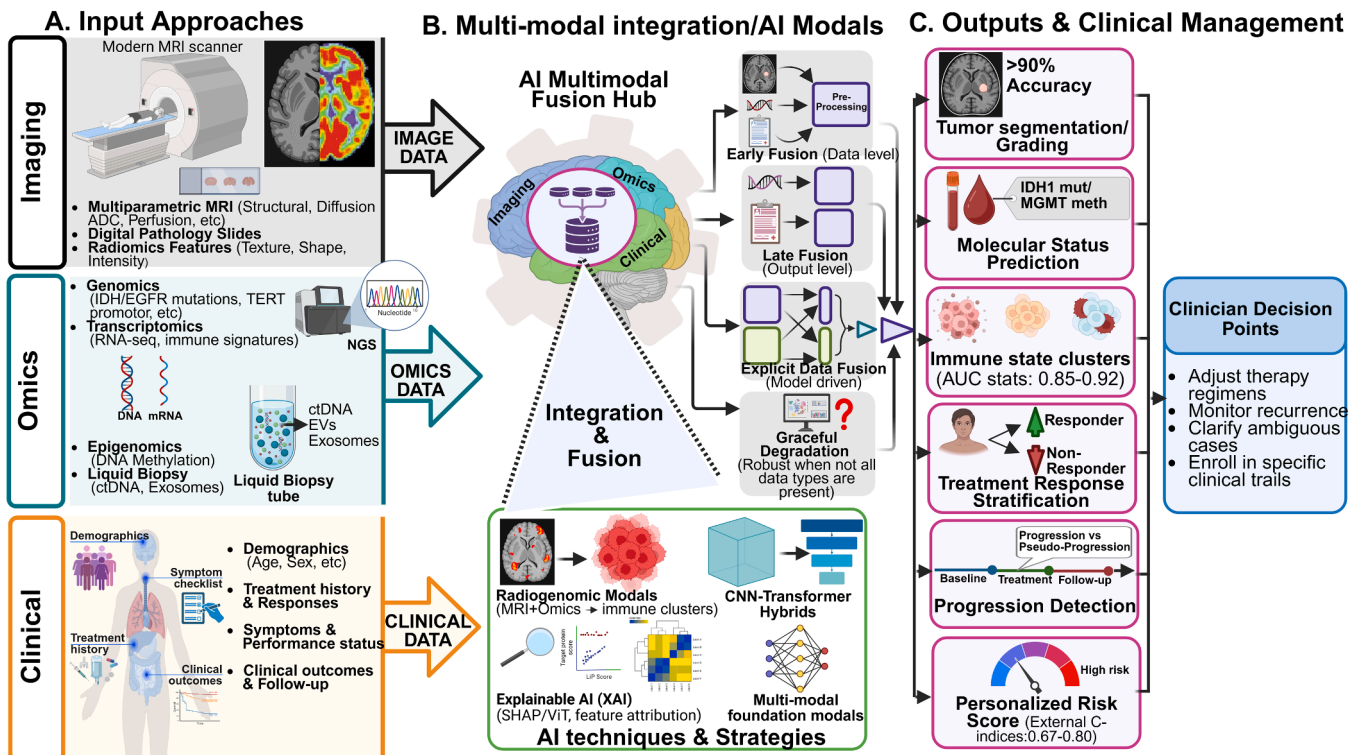


Fig. 2. Multimodal data integration and AI-driven clinical decision support in glioblastoma. (A) Input approaches. Left panels summarize three major input streams used for AI modeling in neuro-oncology. Imaging data includes multiparametric MRI (structural, diffusion, perfusion, susceptibility) and digital pathology slides, from which radiomics features (texture, shape, intensity) are extracted. Omics data encompass genomics (for example, IDH/EGFR/TERT alterations), transcriptomics (RNA-seq, immune signatures), epigenomics (DNA methylation), and LB analytes such as circulating tumour DNA and extracellular vesicles. Clinical data include demographics, treatment history and responses, symptom and performance status measures, and longitudinal clinical outcomes and follow-up. (B) Multi-modal integration/AI models. The central fusion hub illustrates how imaging, omics, and clinical information are combined through integration and fusion strategies. Early fusion operates at the data level, whereas late fusion combines model outputs; explicit data fusion leverages model-driven representations, and “graceful degradation” indicates robustness when some modalities are missing. Example AI strategies include radiogenomic models linking MRI and omics to immune clusters, explainable AI (for example, SHAP, Vision Transformers) for feature attribution, convolutional neural network–Transformer hybrid architectures, and multimodal foundation models that learn shared representations across data types. (C) Outputs and clinical management. Right panels depict key AI-derived outputs and their linkage to clinician decision points. Model outputs include high-accuracy tumour segmentation and grading (>90%), non-invasive molecular status prediction (for example, IDH1 mutation, MGMT promoter methylation), identification of immune state clusters (AUC approximately 0.85–0.92), treatment response stratification of responders versus non-responders, progression detection distinguishing true progression from pseudoprogression across serial scans, and personalized risk scores (external concordance indices roughly 0.67–0.80). These outputs inform concrete clinical actions, including adjusting therapy regimens, monitoring for recurrence, clarifying ambiguous cases, and enrolling appropriate patients into specific clinical trials. This figure was generated using the BioRender software (www.biorender.com).

2.5. Model Validation and Reliability in Brain Cancer Diagnostics

2.5.1. Role of AI in developing advanced sensing platforms for brain cancer diagnosis

AI is becoming the analytical and decision-making layer of advanced sensing platforms for brain cancer diagnosis, particularly glioblastoma. These platforms include optical and spectroscopic sensors, such as Raman, fluorescence and infrared systems; electrochemical and field-effect transistor biosensors; microfluidic and lab-on-a-chip devices; digital pathology and radiological imaging systems; and LB platforms that detect circulating tumour DNA (ctDNA), extracellular vesicles, proteins, metabolites or tumour-associated cells. AI is especially valuable in glioblastoma because tissue access is invasive, requiring neurosurgical biopsy or tumour resection and potentially exposing patients to bleeding, infection and neurological injury; heterogeneity is high, both between patients and within different regions of the same tumour; and intraoperative timing matters, as surgeons may need rapid information to distinguish infiltrating tumour margins from functional healthy brain tissue during resection. Glioblastoma heterogeneity arises from the coexistence of genetically and phenotypically distinct tumour-cell populations, variable expression of diagnostic and therapeutic biomarkers (Table 2a), differences in cellular metabolism, hypoxic and necrotic regions, interactions with immune and stromal cells, and spatial and temporal changes caused by tumour progression or treatment. AI may convert complex outputs, including images, spectra, electrochemical responses, impedance measurements and microfluidic signals, into clinically interpretable diagnostic information. ML and DL models can remove noise and background interference, correct signal drift, segment tumour regions, identify spectral peaks or image patterns, integrate measurements from multiple sensing modalities, and distinguish tumour-associated signals from normal biological variation. AI can also standardise preprocessing, feature selection, thresholds and real-time deployment. Feature selection refers to identifying the most informative variables, such as spectral bands, image textures, biomarker concentrations, electrical-response parameters or temporal signal patterns, while excluding redundant or noisy measurements. Threshold optimisation determines the signal level or predicted probability used to classify a sample or tissue region as tumour-positive, tumour-negative, low-grade or high-grade. Selecting these thresholds is essential for balancing sensitivity and specificity, reducing false-negative results at infiltrative tumour margins, and preventing false-positive classifications caused by inflammation, necrosis or non-specific sensor responses. When incorporated into portable, intraoperative or point-of-care sensing systems, AI may therefore support faster diagnosis, tumour classification, margin assessment, molecular-subtype prediction and treatment monitoring, although clinical implementation requires external validation, interpretable decision outputs and testing across diverse patient populations and healthcare settings [34].

2.5.2. AI as the interpretation layer for high-dimensional sensing

High-dimensional sensing data are rich but noisy. In MRI, radiomics and DL can reveal tumour shape, intensity and texture patterns linked to histology and molecular status, but differences in scanners, imaging protocols and preprocessing can alter these features, making harmonisation and external validation essential [34]. Raman spectroscopy and surface-enhanced Raman scattering (SERS) raise similar issues: label-free biochemical fingerprints are sensitive to baseline drift and variations in sample preparation, laser settings and signal acquisition, requiring machine-learning pipelines for correction, extraction of informative spectral features and classification [35].

2.5.3. Intraoperative sensing: AI enabling near real-time tumour decisions

AI is especially valuable intraoperatively, where conventional pathology can be too slow to guide tumour identification and margin assessment during surgery. Stimulated Raman histology combined with deep neural networks has enabled near-real-time operating-room

classification of fresh tissue as tumour or non-tumour, while portable Raman systems are being explored for rapid margin assessment [36]. Prospective validation across tumour subtypes, institutions, and workflows remains essential.

2.5.4. AI in liquid biopsy sensing: extracting weak signals from blood/CSF biomarkers

LB sensing broadens monitoring beyond the operating room. Brain tumours shed extracellular vesicles, proteins, nucleic acids, and metabolites into blood or CSF, but concentrations are low, partly because the BBB limits their entry into circulation, and sample composition varies between patients. Microfluidic biosensors can enrich rare targets, while ML can denoise signals and identify. Microfluidic biosensors can enrich rare targets, while ML can denoise signals, identify combined biomarker patterns and integrate multiple readouts rather than rely on a single thresholds [37,38]. Translation requires control of sample collection and processing differences, batch effects, and false-positive signals in small cohorts, with outcomes linked to recurrence or treatment response.

2.5.5. AI-guided sensor design and optimization

AI can also accelerate sensor engineering. Bayesian optimization can tune sensing materials, nanostructures geometry, fluid flow and operating parameters, while adaptive filtering and personalized calibration may signal drift in electrochemical or wearable sensors during longitudinal monitoring [39]. For brain cancer diagnostics, success should be judged by robust multicentre performance, clinically relevant sensitivity and specificity, rapid turn around and workflow compatibility, and not analytical accuracy alone.

3. AI in Treatment Planning and Therapeutics

3.1. Personalized Therapy Selection

MRI remains central to brain tumour management, with standard multiparametric sequences (T1 ± contrast, T2, FLAIR) augmented by diffusion, perfusion, and susceptibility imaging [41]. Radiomics extracts quantitative features that capture intra-tumoural heterogeneity for non-invasive molecular characterization, prognostication, and treatment response prediction [42].

For temozolomide (TMZ) response in gliomas, MRI-based radiomics signatures derived from FLAIR and contrast-enhanced T1 images stratify patients by survival benefit, outperforming clinicopathological factors alone [43]. Complementary gene signatures, such as dephosphorylation-related profiles with CDC25A as a key TMZ modulator, provide mechanistic context [44].

MGMT gene promoter methylation (MGMTpm), a major predictor of TMZ response, is increasingly inferred non-invasively from MRI. Early DL models on T2 images showed promise [45], while multiparametric fusion (T1-CE, FLAIR, DWI) and habitat/region-specific extraction (necrosis, edema, enhancing/non-enhancing tumour) improve accuracy [46]. Combining radiomics with MGMT status enhances survival stratification [47]. Recent 3D CNN approaches using mask fusion on BraTS data achieve high AUC (up to 0.90) by incorporating domain knowledge and multi-sequence inputs [48]. MGMT-Net, a multi-task hybrid Transformer-CNN with cross-modality attention, jointly segments tumours and predicts MGMTpm alongside IDH, 1p/19q, and TERT status on BraTS 2024 and TCGA datasets, showing strong generalizability [49] (Table 1).

Volumetric DL-segmented biomarkers, such as larger peritumoural edema in MGMT-methylated high-grade gliomas, correlate with survival and treatment sensitivity [50]. Multimodal DL integrating radiomics, clinical variables, molecular markers (MGMT, IDH), and treatment data yields superior overall survival prediction in glioblastoma after chemoradiotherapy [51].

In anti-angiogenic therapy with bevacizumab, multiparametric

radiomics predict response and survival more effectively than clinical or volumetric metrics [52]. Multimodal frameworks combining radiomics with clinical and molecular data consistently outperform unimodal models across cohorts, although translation is limited by dataset heterogeneity and validation requirements [53].

Advanced models further demonstrate progress. Dense NN approaches on multi-institutional *IDH*-wildtype glioblastoma cohorts (UPENN-GBM, UCSF-PDGM) integrating radiomics, clinical variables, and MGMT data achieve high concordance indices (0.83–0.86) for survival prediction [54]. Temporal DL on serial MRI improves 1-year recurrence prediction in pediatric gliomas through self-supervised pre-training, with performance gains plateauing after 3–6 scans [55]. Dual-path networks (MDPNet) and multitask frameworks (Multi-CubeNet) predict *IDH*, 1p/19q, *ATRX/TERT* status, and prognosis from multimodal MRI, surpassing conventional radiomics and supporting integrated genotyping and prognostication [56,57]. Multimodal fusion of histopathology and genomics enhances prognostic modelling, with joint strategies generalizing via transfer learning [58]. Radiomics-based models predict IL7R expression-linked poor outcomes and immune features in high-grade gliomas [59]. SLC family signatures stratify risk, correlate with immunosuppression, and inform immunotherapy or drug sensitivity [60]. ML frameworks using gene panels predict immune checkpoint inhibitor benefit in glioblastoma with high AUC for responders [61]. Microbiota-gut-brain axis analyses identify microbe-related signatures for prognosis and potential immunotherapy stratification [62].

Collectively, MRI-radiomics, DL, and radiogenomics enable non-invasive molecular and therapeutic insights, but prospective multi-centre validation and standardization remain essential for routine clinical adoption.

3.2. Surgical Planning and Navigation

AI enhances neurosurgical precision in glioblastoma through automated segmentation and intraoperative guidance. Multimodal MRI models achieve high Dice scores > 0.90 for tumour core, peritumoural edema, and infiltrative margins, supporting 3D volumetric planning aimed at maximal safe resection. Explainable AI tools can predict the achievable extent of resection, with human-AI collaborative approaches often outperforming experts alone in decision-making tasks [63]. Intraoperative integration of tools such as intraoperative MRI (iMRI), 5-aminolevulinic acid (5-ALA) fluorescence, ultrasound, and augmented reality (AR) overlays helps correct for brain shift and may reduce the risk of damaging eloquent tissue (reported reductions of approximately 30% in selected studies using specific functional endpoints such as post-operative neurological deficit rates or Karnofsky performance status preservation). However, these benefits are context-dependent, and broader prospective multicentre data on long-term functional outcomes, workflow integration, cost-effectiveness, and generalizability are still needed.

Additional applications include 3D CNNs for mapping functional networks from abbreviated fMRI, as well as DL-optimized trajectories in robotic neuroendoscopy and tubular retractors for minimally invasive access to deep or midline tumours [64]. Overall, while promising, these AI-assisted navigation technologies should be viewed as decision-support tools within multidisciplinary teams rather than fully autonomous systems, with rigorous prospective validation required before widespread routine adoption.

3.3. Drug Discovery and Repurposing for Brain Cancers

As outlined in the previous sections, the aggressive nature of brain cancer, together with therapeutic limitations, treatment-associated resistance, and high rates of post-therapy recurrence, underscores the urgent need for a comprehensive and strategically integrated clinical approach from diagnosis to treatment. The integration of AI into

oncology research and clinical practice is increasingly recognized as essential for overcoming these challenges. AI-based models facilitate early diagnosis, predictive biomarker discovery, and rational drug design, thereby enhancing therapy development and enabling personalized treatment strategies. These computational frameworks may ultimately bridge the gap between laboratory discoveries and clinically effective interventions.

3.3.1. Target and pathway prioritisation

The first step in developing AI-guided therapeutic strategies for brain cancer is a comprehensive and multidimensional evaluation of available datasets. The central question must be clearly defined: Which clinical problem is to be addressed? Key considerations include resistance to a defined therapy (e.g., TMZ), recurrent glioblastoma, the influence of mutational heterogeneity on disease progression, whether the target is prognostic or predictive, and whether the condition is therapeutically actionable. These questions must be addressed within the constraints of existing datasets, as the clinical relevance and translational impact of AI-driven models depend on precise problem definition.

Biological systems and disease phenotypes arise from complex interactions across multiple omics layers. Conventional statistical frameworks often lack the capacity to effectively interrogate high-dimensional, heterogeneous, and nonlinear datasets. AI-assisted integration of genomic, transcriptomic, proteomic, metabolomic, and radiomic data enables the identification of disease-associated molecular signatures and the reconstruction of systems-level regulatory networks [66]. These networks provide critical insights into pathway dysregulation and enhance the discovery of actionable therapeutic targets (Fig. 3A).

In contrast to conventional omics integration, AI-driven methodologies demonstrate superior robustness in handling complex, high-dimensional datasets. Network-based approaches and ML-driven algorithms are widely employed. Network-based methods leverage established biological interaction maps to identify disease-relevant modules and prioritize targets with strong mechanistic interpretability [67], whereas ML-driven frameworks extract predictive patterns to model drug response, disease subtypes, and patient-specific outcomes (Fig. 3B) [68].

glioblastoma exhibits pronounced intra-tumoural heterogeneity driven by malignant cell plasticity and the dynamic influence of the tumour microenvironment [69]. Treating tumour tissue as homogeneous can introduce substantial bias in target identification. This can be mitigated by incorporating tumour purity and immune/stromal proportions as covariates through computational deconvolution, as demonstrated by Neftel *et al.* [70]. State-resolved analyses of malignant cell states and longitudinal study designs, as highlighted by Varn *et al.* [71], further improve biological specificity and clinical relevance. Re-annotating samples according to the WHO CNS5 (2021) classification [12] and stratifying molecular subgroups prior to integration substantially enhances the robustness of downstream analyses.

3.3.2. AI-driven drug discovery

Multi-omics integration enables the identification of specific molecular targets for therapeutic candidates (Fig. 3). The drug design stage remains highly labor-intensive using conventional methodologies, often requiring multiple iterative experimental cycles that increase costs and prolong development timelines.

Conventional strategies include (i) virtual screening of large chemical libraries [72]; (ii) structure-activity relationship (SAR)-based design [73]; and (iii) receptor structure-based design exploiting the three-dimensional architecture of druggable sites [74]. These approaches are largely hypothesis-driven and expert-dependent.

Artificial intelligence was initially integrated into computer aided drug design (CADD) to optimize SAR strategies through quantitative structure-activity relationship (QSAR) models [75]. Modern AI methodologies including ML, DL, natural language processing (NLP),

Box 2**Key challenges for translation and how AI can help?**

Translation remains constrained by small datasets, overfitting, domain shift, inconsistent labelling, batch effects, sensor aging, and insufficient external validation; these issues are repeatedly noted across glioma AI, spectroscopy, and biosensor studies and reviews [34,35,37,38]. Domain shift occurs when patient populations, instruments or clinical workflows differ from those used to train the model, while sensor ageing can cause gradual signal drift. Poorly designed or biased models can amplify errors, while transparent reporting and rigorous evaluation are often lacking. AI counters these risks through domain adaptation, uncertainty quantification, interpretable attribution, confidence and uncertainty estimates, continual learning for post-deployment monitoring, and clinically grounded validation. The most promising path forward prioritizes integration into multimodal, decision-support workflows combining imaging, biofluid sensors, and clinical context over standalone black-box systems, ensuring reliable, trustworthy performance in real-world neuro-oncology practice [40].

reinforcement learning (RL), and quantum computing-assisted approaches [76] have markedly improved predictive accuracy for binding affinities and drug-target interactions (Fig. 2C). AI-driven docking frameworks utilize neural network architectures to predict ligand conformations and generate energetically favorable binding poses with greater reliability than traditional scoring functions [77]. These techniques enhance the overall reliability and efficiency of computational drug design compared with conventional approaches [78].

When conducted in parallel with multi-omics data integration, AI-driven drug design facilitates rapid identification and optimization of candidate compounds against well-validated targets. Recent studies have applied these strategies to brain cancer [79,80].

Drug repurposing, a major AI application, identifies new indications for approved drugs with established safety profiles. While successful in well-characterized diseases, its effectiveness is substantially diminished in conditions with marked heterogeneity and limited clinically annotated omics datasets, such as rare diseases [81].

3.3.3. Brain-specific filters

Designed compounds must exhibit not only target-specific efficacy but also key drug-likeness properties, including solubility, toxicity, metabolic stability, and membrane permeability [82]. Compound libraries are typically pre-filtered for these properties before virtual screening.

For brain cancer therapeutics, additional challenges arise from the BBB and blood–tumour barrier (BTB) (Fig. 3C). Early approaches relied on Lipinski's Rule of Five [83], yet BBB permeability is far more complex, involving molecular conformation, transporter activity, and protein interactions [84].

Recent AI-driven models trained on large-scale datasets capture nonlinear relationships more effectively than rule-based methods. These models utilize molecular descriptors (MDs), fingerprints (FPs), and SMILES strings [85]. Algorithms such as support vector machines (SVM) [86], Random Forest [87], XGBoost [88], graph neural networks [89], and transformer-based models [90] predict BBB permeability metrics, including binary classification (BBBp) and logBB [91].

Important pharmacokinetic parameters include the brain-to-plasma ratio ($K_{p,brain}$) [92] and the unbound brain-to-plasma ratio ($K_{p,uu,brain}$). Under steady-state conditions, $K_{p,uu,brain,ss}$ values near 1 indicate passive diffusion, while deviations suggest active transport or efflux [93]. AI-driven CADD frameworks thus enable rapid assessment of CNS penetration potential across large chemical libraries prior to experimental validation.

Despite AI successes across cancers, a major bottleneck in brain cancer research is the limited availability of harmonized, clinically well-annotated multi-omics datasets [94]. Model performance is often constrained more by data quality than algorithmic complexity. Rigorous data source selection, multi-omics integration, quality control should be performed to prevent label leakage, de novo design strategies, and brain-tailored filtering pipelines form the core of an effective AI-enabled drug development workflow.

4. AI for Patient Monitoring and Prognosis

In brain tumours, surveillance must distinguish true progression from treatment-related change and detect neurological decline early enough to alter care. MRI and tissue sampling remain episodic, and most AI evidence is retrospective. Technical discrimination should not be equated with clinical benefit: an externally tested AUC or Dice score does not show that a tool improves re-imaging, LB and TB, treatment adaptation, or trial referral. Clinically useful systems should update risk over time, quantify uncertainty, and be evaluated at prespecified decision thresholds.

4.1. Disease Progression Prediction

Progression assessment begins with reproducible quantification of enhancing and non-enhancing disease. Gagnon *et al.* [95] developed a nnU-Net using multimodal MRI, including perfusion and multiscale diffusion. In 178 internal patients and four external cohorts, median Dice scores were 0.79 and 0.73, respectively; the distinguishing residual or recurrent tumour from treatment change (internal AUC 0.84; external AUC 0.91), and cellular-tumour volume was associated with survival. These retrospective associations support analytical validity, but do not establish that automated contours improve decisions or outcomes.

Post-radiotherapy MRI remains difficult because enhancement, oedema, and necrosis may reflect tumour or treatment effect or both. Yadav *et al.* [96] combined diffusion and perfusion features with *MGMT* promoter methylation in 75 patients; a quadratic support-vector machine reached 85% accuracy (specificity 100%, sensitivity 70%, AUC 0.84) for distinguishing pseudoprogression from true progression. Goma *et al.* [97] used self-supervised pretraining on 2317 unlabelled glioma MRIs and fused routine MRI with clinical and radiotherapy data; in an independent 20-patient test cohort, the AUC was 0.753. External testing is important, but the small cohorts, class imbalance, and absence of prospective impact evaluation preclude using either model as a stand-alone trigger for biopsy or treatment change.

Large-scale automation also exposes failure modes. In 634 patients with 3403 MRIs, automated volumetric response assessment showed only moderate agreement with radiologists (F1 0.587–0.755) and weaker survival stratification than human assessment [98], indicating that response categories encode symptoms, steroid exposure, and treatment history that imaging alone may not capture. Conversely, a prospective single-centre study of 79 patients with IDH-wildtype glioblastoma used serial diffusion and perfusion MRI to derive spatiotemporal tumour habitats: its risk score predicted 12-month time to progression better than volume (AUC 0.762 vs 0.646), although localisation of later progression was modest (mean Dice 0.31) [99]. Preoperative MRI plus clinical variables yielded a time-dependent concordance of 0.85 for recurrence risk in paediatric low-grade glioma [100]. These observational studies improve temporal stratification, but have not shown that model-guided surveillance improves outcomes. Hybrid modelling brings biological constraints into forecasting.

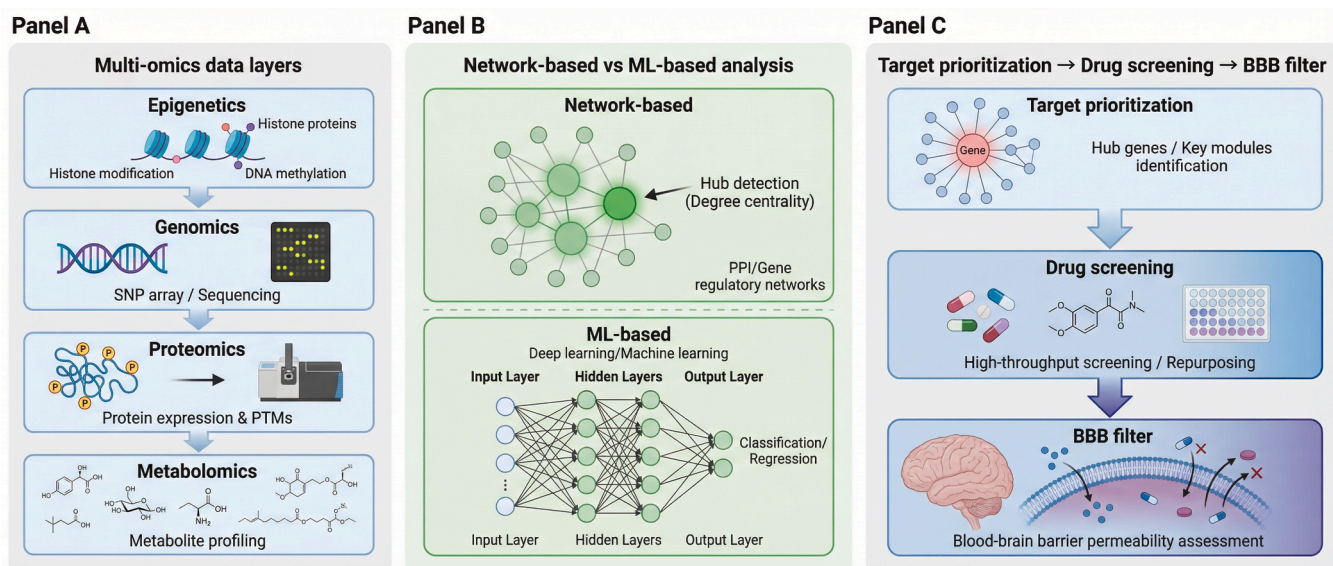


Fig. 3. AI-based identification of therapeutic targets and brain-penetrant candidates. Panel A: Multi-omics data layers showing the four key omics disciplines (Epigenetics, Genomics, Proteomics, and Metabolomics) with representative icons. Panel B: Network-based vs ML-based analysis comparing the two AI approaches with visual representations of network analysis and neural networks. Panel C: Target prioritization → Drug screening → BBB filter. The workflow from target identification through drug screening to blood-brain barrier filtering. This figure was generated using the Skywork application (<https://skywork.ai/>).

Physics-informed neural networks (PINNs) inferred infiltration and proliferation from MRI and improving tumour-distribution fit relative to conventional inversion (Dice approximately 0.68 vs 0.41) [101]. GliO-DIL optimised a data- and physics-informed discrete loss to estimate occult cell concentration, but increased retrospective recurrence coverage within radiotherapy targets only modestly (70.04 – 72.94% when fluoroethyltyrosine PET was added) [102]. Such models make assumptions explicit, yet parameter identifiability, segmentation error, calibration, and uncertainty propagation remain unresolved. Prospective studies should compare them with standard follow-up using pre-specified action thresholds and decision-curve analysis rather than discrimination alone.

4.2. Remote Patient Monitoring and Digital Health Tools

Follow-up also requires information between scans. Electronic patient-reported outcomes (ePROs), wearables, and smartphones can capture seizures, fatigue, cognition, sleep, mood, mobility, steroid use, and caregiver concerns at higher frequency than clinic visits. Passive smartphone geolocation data quantified perioperative mobility in 15 patients with glioblastoma [103], while a 54-patient feasibility study collected sleep and activity data with smart wearables alongside patient reports [104]. Neither study trained or prospectively validated an AI system for deterioration prediction; the evidence therefore supports feasibility and phenotyping, not clinical effectiveness. Evidence that remote monitoring changes care comes mainly from broader oncology. In a non-randomised implementation study of 5949 patients, 1392 receiving ePRO-based monitoring had 19% fewer hospitalisations at 3 months and 13% fewer at 6 months than historical controls, whereas emergency-department and intensive-care use did not differ significantly [105]. The design and non-neuro-oncology population limit causal and disease-specific inference. Brain-tumour programmes must accommodate cognitive or language impairment, caregiver-mediated reporting, informative missingness, digital exclusion, privacy, alert fatigue, staffing, interoperability, and reimbursement. Prospective studies should define who reviews alerts and test actionable outcomes such as appropriate imaging escalation, toxicity reduction, hospitalisation, quality of life, and equity rather than engagement alone.

4.3. Multimodal Integrative Models

Multimodal integration is most useful when it resolves a defined clinical ambiguity rather than merely concatenating features. In paediatric low-grade glioma, multiparametric MRI plus RNA sequencing identified immune clusters; diffusion features predicted immune phenotypes (AUC 0.83 and 0.79), and clinicoradiomic risk models were associated with treatment resistance (concordance 0.71–0.77) [106]. In 2776 adult gliomas, an imaging-first multi-task network predicted molecular alterations, grade, and prognosis, with external C-indices of 0.67–0.72 [107]. Both studies show the potential of biologically informed fusion, but remain retrospective and sensitive to cohort and acquisition differences.

Explicit fusion can improve prediction, but external performance is heterogeneous. GliSurv integrated MRI, clinical and molecular variables, and treatment data across 1944 patients, with external C-indices ranging from 0.61 to 0.80 [108]. A 2026 multicentre study of 1883 patients combined a vision-transformer imaging index with clinical and molecular variables; C-indices were 0.77 internally and 0.73 and 0.63 in two external cohorts, compared with 0.73, 0.65, and 0.60 for imaging alone, while time-dependent Shapley explanations showed how variable contributions changed over the survival horizon [109]. The external decline illustrates domain shift and cautions against assuming that more modalities guarantee portable benefit. Longitudinal single-cell studies further show that malignant states and microenvironmental programmes evolve differently across patients [110], so static risk estimates require updating.

Deployable multimodal systems should handle informative missingness, remain calibrated across sites, expose modality-specific contributions, and report uncertainty at clinically meaningful thresholds. Serial circulating biomarkers may complement imaging when results disagree, but low analyte abundance, blood–brain barrier constraints, clonal haematopoiesis, and pre-analytical variability mean that LB should remain an adjunct to imaging and tissue diagnosis rather than a replacement [21,22,24,111]. Reporting should follow TRIPOD + AI [112] and evaluation should include external validation, calibration, decision-curve analysis, subgroup performance, workflow feasibility, and prospective clinical-impact studies (Table 2b). Prospective evidence that such systems improve outcomes in brain-tumour care remains

Box 3**Future directions.**

Future AI systems in brain tumours should be designed as adaptive clinical infrastructure rather than isolated prediction models. Multimodal foundation models trained on large imaging, pathology, and molecular repositories could support transfer learning for rare tumour subtypes, provided that pretraining data provenance, bias, and failure modes are disclosed [124]. Self-supervised and federated learning can improve generalisation while protecting privacy, but they require common data models, harmonised imaging and omics pipelines, and prospective drift monitoring. Real-time decision support is likely to expand from automated segmentation and surgical navigation to progression alerts, trial matching, and toxicity surveillance; these tools must be embedded within electronic health records and picture archiving systems rather than added as parallel dashboards [125]. Synthetic data generated by diffusion models or generative adversarial networks may help address class imbalance, but these should be used cautiously, and any clinical use will require formal privacy-risk assessment and evidence that augmented data do not amplify artefacts [126]. AI-supported trial design, including virtual cohorts, adaptive enrichment, and automated patient matching, could accelerate testing of brain-penetrant drugs and biomarker-defined therapies [118]. Finally, hybrid models that combine causal inference, mechanistic tumour-growth models, and DL may provide more transparent counterfactual predictions than purely associative systems [127]. In this regard, hybrid data- and model-drive systems can improve the biological or visual interpretability of any ML prediction, making an AI system more trustworthy at the expense of a negligible loss of accuracy. Overall, the field should now prioritise open benchmarks, health-equity audits, patient-centred endpoints, and implementation studies that ask whether AI improves decisions, outcomes, and access to specialist neuro-oncology care.

lacking.

5. Challenges and limitations

Despite significant progress, AI implementation in brain cancer management encounters substantial obstacles [44]. Neuro-oncology datasets are constrained by small cohort sizes stemming from low disease incidence, class imbalance in rare subtypes, and incomplete multimodal annotations such as mismatched imaging-omics pairs [113]. These factors promote overfitting and restrict generalizability across centres. Heterogeneity from variable imaging protocols, scanner differences, and inherent tumour biology frequently causes domain shift, where models perform adequately on internal data but degrade on external or real-world cases [114]. Public benchmarks like BraTS provide useful standardization but often fail to reflect full clinical variability [115]. Specific real-world failures illustrate these issues. Several radiomics and DL models that achieved high accuracy in single-centre retrospective cohorts showed substantial performance drops (e.g., AUC decline of 0.15–0.25 or Dice score reductions of 8–15%) upon external validation, primarily due to scanner variability, differences in acquisition protocols, and domain shift [40,116]. Black-box models have also led to reduced clinician trust when explanations did not align with known biology or when saliency maps appeared inconsistent, contributing to low adoption rates in some institutions [117]. Bias in training data arising from demographic underrepresentation, labeling inconsistencies, or selection effects can perpetuate disparities in model performance across diverse populations [64].

Additional practical barriers include workflow integration (e.g., compatibility with existing hospital PACS/EMR systems), reimbursement models (many AI tools lack clear CPT codes or payer coverage), high computational costs for real-time inference, and equity gaps, models trained predominantly on data from high-resource settings often underperform in low- and middle-income countries [51,118].

The black-box nature of many DL models undermines clinical trust by obscuring the rationale behind decisions, and while post-hoc explainability techniques such as SHAP and LIME offer partial mitigation, they remain computationally intensive and incomplete [119]. Regulatory pathways, including FDA Software as a Medical Device (SaMD) guidelines, require prospective validation, yet the majority of published studies are retrospective [51].

Reproducibility is further hampered by unreported hyperparameters, inconsistent preprocessing pipelines, and the absence of standardized benchmarks. Federated learning provides a pathway for privacy-preserving multi-site training, but it scales poorly with highly heterogeneous data [120]. Ethical considerations include obtaining

informed consent for AI training data and clarifying liability in cases of erroneous predictions. Finally, seamless integration into clinical workflows demands intuitive user interfaces, real-time inference on hospital hardware, and well-defined human-AI collaboration protocols capabilities that most current systems still lack (Fig. 1). Overcoming these interconnected challenges will require sustained interdisciplinary collaboration focused on high-quality data curation, rigorous external validation, harmonised regulatory standards, health equity audits, and implementation science studies that evaluate real-world effectiveness and cost-benefit.

6. Broader Context: AI in Surgical Oncology and Multidisciplinary Care

Beyond neuro-oncology, artificial intelligence is increasingly being investigated across the broader landscape of surgical oncology as a tool to support diagnosis, risk stratification, and multidisciplinary decision-making, and these parallel experiences provide a useful comparative framework for the present review. In gastric cancer surgery, AI applications range from AI-assisted endoscopic detection and intraoperative recognition of anatomical structures to data-driven perioperative risk prediction, positioning AI as a component of contemporary surgical practice while highlighting the continued need for structured validation processes, sustained human oversight, and clearly defined medico-legal accountability [121]. Similarly, in hepatopancreatobiliary oncologic surgery, one of the most complex domains of oncologic care given its substantial risk-benefit considerations, recent systematic review demonstrated that AI has shown potential in predicting clinically relevant outcomes such as malignancy likelihood, postoperative complications, and long-term survival; however, the evidence base remains limited by small sample sizes, retrospective designs, and a scarcity of prospective validation in real-world clinical settings [122]. At the level of cancer care coordination, AI is also being progressively integrated into multidisciplinary tumor boards (MTBs), reflecting its growing traction across surgical, medical, and radiation oncology specialties; AI-based clinical decision support systems, such as Watson for Oncology, have been employed to evaluate patient-specific clinical data against a broad spectrum of evidence, including the medical literature, treatment guidelines, and pharmacologic information, thereby assisting, rather than substituting, the multidisciplinary team in treatment planning [123]. Collectively, these examples from gastric cancer surgery, hepatopancreatobiliary oncology, and tumor board decision-making illustrate a consistent trajectory within surgical oncology, whereby AI tools are progressively transitioning from isolated diagnostic aids toward integrated, multidisciplinary decision-support platforms. This trend

provides an important contextual backdrop against which the emerging role of AI in neuro-oncologic surgeries, as discussed in the present review, can be more comprehensively situated.

7. Conclusion

AI offers transformative potential in brain cancer management by enabling non-invasive diagnostics, personalized therapy selection, precise longitudinal monitoring, and enhanced surgical navigation capabilities especially vital for aggressive tumours like glioblastoma [44] (Fig. 1). Through multimodal integration and sophisticated predictive modelling (Fig. 2), AI can reveal latent patterns within sparse and heterogeneous data, supporting earlier detection, more accurate prognostication, adaptive interventions, and ultimately improved survival and quality of life [113]. Widespread clinical adoption, however, hinges on resolving persistent limitations: data scarcity and bias, model robustness and explainability, regulatory compliance, and practical workflow integration [64,114]. Prospective multi-centre validation, privacy-preserving federated learning approaches, and well-designed human-AI collaborative frameworks will be essential to bridge the gap from research to routine practice [51,120]. When these foundational challenges are addressed, AI can help usher in a true era of precision oncology for brain tumours.

CRediT authorship contribution statement

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Declaration of Competing Interest

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Glossary

CNN (Convolutional Neural Network): A DL architecture specialized for processing grid-like data such as images. It uses convolutional layers to automatically extract hierarchical spatial features (e.g., edges, textures, tumour boundaries) from MRI, PET, or whole-slide pathology images, making it highly effective for tasks like tumour segmentation, classification, grading, and pseudoprogression detection in brain cancer diagnostics.

ctDNA (circulating tumour DNA): Tumour-derived DNA fragments released into blood or CSF, enabling non-invasive LB detection of mutations (e.g., IDH, EGFRvIII, TERT) for molecular profiling, treatment monitoring, and progression assessment.

Deep Learning (DL): Subset of ML employing multi-layered neural networks (including CNNs and Transformers) to learn complex patterns directly from raw data, powering most modern AI applications in neuroimaging, pathology, and multimodal fusion for brain tumours.

Federated Learning: Decentralized training method that builds models across multiple institutions without exchanging raw patient data, preserving privacy while addressing data scarcity and heterogeneity in neuro-oncology.

Foundation Models: Large-scale, general-purpose AI models pretrained on massive datasets (e.g., imaging, genomics) and adaptable via fine-tuning or few-shot learning for specialized tasks like rare glioma subtyping or cross-site generalization.

Glioblastoma: Most aggressive primary brain tumour (WHO grade 4), featuring rapid infiltration, high heterogeneity, and dismal prognosis (median survival ~9–15 months) despite surgery, radiotherapy, and temozolomide.

IDH (Isocitrate Dehydrogenase): Key diagnostic/prognostic marker; IDH mutations define lower-grade gliomas and secondary glioblastoma, associated with better outcomes and used in 2021 WHO classification.

Liquid Biopsy: Minimally invasive analysis of biofluids (blood, CSF) for tumour-derived biomarkers (ctDNA, EVs, proteins) to enable non-invasive molecular diagnosis, monitoring, and therapy guidance.

MGMT Promoter Methylation: Epigenetic modification predicting improved response to temozolomide and longer survival in glioblastoma.

Multimodal Integration: AI-driven fusion of diverse data (MRI radiomics, digital pathology, genomics, clinical variables) to capture tumour complexity and enhance diagnostic/prognostic accuracy.

Physics-Informed Neural Networks (PINNs): Neural networks constrained by physical equations (e.g., reaction-diffusion) to model tumour growth/infiltration from sparse imaging, supporting personalized radiotherapy planning.

Pseudoprogression: Treatment-induced MRI changes mimicking true tumour progression; accurate differentiation is critical and increasingly supported by AI models.

Radiomics: Quantitative extraction of high-dimensional features (texture, shape, intensity) from medical images to generate non-invasive biomarkers for tumour phenotyping, grading, and molecular prediction.

RANO (Response Assessment in Neuro-Oncology): Standardized MRI-based criteria for evaluating brain tumour treatment response, incorporating tumour measurements, clinical status, and steroids.

SRH (Stimulated Raman Histology): Label-free optical imaging providing rapid, intraoperative histological visualization; combined with DL for near real-time tumour diagnosis and margin assessment.

Transformer Models / ViT (Vision Transformer): Attention-based architecture that processes entire images (or sequences) globally by focusing on relevant regions via self-attention, outperforming CNNs in many tasks like glioma subtyping, multimodal fusion, and survival prediction due to superior capture of long-range dependencies.

Whole-Slide Imaging (WSI): High-resolution digitization of entire pathology slides, enabling AI analysis for automated grading, molecular marker inference (e.g., IDH from H&E), and tumour microenvironment mapping.