

Value of artificial intelligence in neuro-oncology

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CNS cancers are complex, difficult-to-treat malignancies that remain insufficiently understood and mostly incurable, despite decades of research efforts. Artificial intelligence (AI) is poised to reshape neuro-oncological practice and research, driving advances in medical image analysis, neuro-molecular-genetic characterisation, biomarker discovery, therapeutic target identification, tailored management strategies, and neurorehabilitation. This Review examines key opportunities and challenges associated with AI applications along the neuro-oncological care trajectory. We highlight emerging trends in foundation models, biophysical modelling, synthetic data, and drug development and discuss regulatory, operational, and ethical hurdles across data, translation, and implementation gaps. Near-term clinical translation depends on scaling validated AI solutions for well defined clinical tasks. In contrast, more experimental AI solutions offer broader potential but require technical refinement and resolution of data and regulatory challenges. Addressing both general and neuro-oncology-specific issues is essential to unlock the full potential of AI and ensure its responsible, effective, and needs-based integration into neuro-oncological practice.

Introduction

Primary CNS tumours are the second most common cancers in adolescents and young adults and the eighth most common cancer in older adults.¹ Secondary CNS tumours—ie, brain metastases—are the most common type of brain tumour, affecting 10–26% of individuals who die from cancer.² The associated burden on the health-care system is substantial owing to the high morbidity and mortality rates in affected individuals.^{1,2} Overall, CNS neoplasms have a poor prognosis, as their unique and complex pathomechanisms hinder the development of effective therapies.

Advances in precision diagnostics and assessments,^{1,3,4} therapeutic options,^{5,6} and translational neuroscience—particularly the emerging field of cancer neuroscience^{7,8}—have been accompanied, and, in part, enabled by remarkable innovations in machine learning, including foundation model-based applications.^{9,10} A plethora of artificial intelligence (AI) studies in neuro-oncology highlight the potential of AI in assisting neuro-oncologists across the entire care spectrum and providing scientific insights into the complexities of CNS tumours (figure 1). However, the clinical applicability of AI in neuro-oncology hinges on

understanding the specific capabilities and limitations of every method, including where and how the methods can be used (panel 1). In this Review, we discuss specific AI applications across the neuro-oncological care trajectory—from prevention to rehabilitation—along with associated challenges and limitations, and the emerging opportunities that have yet to permeate translational and clinical neuro-oncology (for in-depth discussions of specific topics, see resources listed in the appendix [p 3]).

Epidemiology and prevention

Primary CNS tumours have a global age-standardised incidence rate of 4–63 per 100 000 person-years;¹² brain metastases of common systemic cancers (lung, breast, prostate, melanoma) occur with an estimated incidence of 9–17%.² The prevention of primary brain tumours is exceptionally difficult given the low numbers of actionable oncogenic germline mutations.^{1,13} Besides ionising radiation exposure and rare hereditary syndromes, no other risk factors, including smartphone use, have been conclusively identified.¹ Nonetheless, the growing wealth of molecular data from pan-cancer whole-genome sequencing studies,¹³ along with advances in modelling higher-order molecular

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Search strategy and selection criteria

References for this Review were identified from searches of PubMed, ArXiv, and Google Scholar with predefined MeSH term-based search phrases and terms, including “glioma”, “glioblastoma”, “machine learning”, “radiomics”, “foundation model”, and “omics”, from Jan 1, 2020, to Dec 7, 2024. We built python wrappers around the PubMed and ArXiv APIs to automate retrieval of article title, abstract, publication date, authors, affiliations, journal, number of citations, and DOI (appendix p 1). Due to legal restrictions on automated retrieval from Google Scholar, the corresponding search was performed manually. English articles were screened for relevance based on exclusion and inclusion criteria, defined separately for clinical and experimental studies (appendix pp 1–2). Due to the large number of studies and reference constraints, preference was given to multicentre clinical studies with large patient cohorts, studies representative of key emerging trends within medical artificial intelligence or neuro-oncology, and those published in high-impact journals. After two rounds of screening, 275 publications were evaluated in depth. After the exclusion of 234 articles and manual addition of 11 articles of high relevance, 52 original articles were included (figure 2). The distribution of papers per category is shown in figure 3. The current literature is dominated by studies on clinical imaging and radiomics as well as deep learning and classic statistical methods, which are also prominently used for omics studies; few studies have investigated niche modalities and advanced techniques (figure 3).

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See Online for appendix

interactions and inferring molecular traits from non-invasive imaging biomarkers, suggests future AI use in predicting clinico-molecular risk factors. For instance, AI-based brain metastasis risk scores derived from bulk RNA-seq data have revealed metastasis-associated epithelial cells in primary lung adenocarcinoma as potential metastatic origins.¹⁴ Given the high brain metastasis incidence rates, similar risk stratification approaches might inform screening and CNS prophylaxis strategies.

Early detection and diagnosis

Imaging-based diagnosis

MRI is routinely used to detect and assess disease type, location, and extent via macrostructural anatomical information provided by pre-contrast and post-contrast-enhanced T1-weighted and T2-weighted MRI.¹ Structural MRI-trained AI models have been used across all standard preprocessing and diagnostic tasks, including denoising, registration, artifact correction, tumour detection, segmentation, classification, and grading.^{15–18} AI-assisted diagnosis might reduce difficulties associated with the detection of lesions of small size, heterogeneity, and ambiguous clinical-radiographic presentation, mitigating inter-rater variability and risks from invasive diagnostic procedures.¹⁸ Multicentre studies recently showed that deep learning-informed CNS tumour detection and classification improves the classification accuracy and volumetric assessment of neuroradiologists.^{15,18} However, in most instances, performance is only shown in small, homogeneous cohorts, and prospective, continuous, and multicentre validation and consecutive translation into clinical practice remain largely unmet needs.¹ Although most applications are developed for well delineated tasks on a single imaging modality, models simultaneously trained on multiple modalities or for multiple tasks are increasingly emerging, with initial results suggesting non-inferiority to unimodal models on selected neuro-oncological tasks.¹⁷

Besides tumour type, grade, and extent visible on clinical imaging, the molecular-genetic and metabolic profiles of primary CNS tumours, brain metastases, and treatment-related adverse effects profoundly affect management strategy and prognosis,^{1,19} as reflected in the revised WHO classification of tumours of the CNS published in 2021.¹⁹ Hence, AI-based translational inference of molecular characteristics from structural neuroimaging data has garnered considerable interest as a cost-effective, non-invasive alternative to conventional tissue-based diagnosis.^{16,20,21} Radiomics (extraction of predefined quantitative medical image descriptors), radiogenomics (radiomics-based prediction of molecular traits), and, more recently, deep learning (panel 1) have shown promise in predicting clinically relevant genetic alterations (eg, isocitrate dehydrogenase mutation and 1p/19q co-deletion) and epigenetic profiles (eg, O⁶-methylguanine-DNA methyltransferase [MGMT] promoter methylation status) from structural and diffusion-weighted MRI^{17,20} and 6-¹⁸F-fluoro-L-DOPA PET.²¹

Although radiomics or learned features used for translational inference sometimes have morphological or clinical correlates, the data-driven nature of AI necessitates tissue-based corroboration and biological annotation to validate imaging-based studies for improved clinical utility.²² This approach can entail molecular annotation of AI-extracted features via correlation with histological or immunohistochemical traits—eg, tumour immune microenvironment macrophage infiltration²³ or tumour subtype-specific differentially modulated pathways potentially implicated in pathogenesis.^{24,25}

Beyond neuroimaging-informed prediction of histomolecular tissue properties via translational inference, AI might catalyse the utilisation of non-standard or non-human-interpretable imaging modalities—eg, ultrasound radio frequency signals for intraoperative molecular glioma diagnosis²⁶ or glioma grade-specific cerebrovascular dysregulation biomarkers extracted from blood oxygen level-dependent functional MRI.²⁷

If data are noisy, scarce, or unavailable, generative models can be trained to produce synthetic images, such as super-resolved magnetic resonance spectroscopy images for improved metabolic characterisation of isocitrate dehydrogenase-mutant gliomas¹⁶ or post-contrast structural MRIs generated de novo from pre-contrast images for CNS tumour grading.²⁸ However, a lack of underlying mechanistic or causal models present a fundamental upper bound to the explanatory power of association-based approaches. Instead, biophysical or physics-constrained models of medical image generation processes might not only produce realistic synthetic data but also confer causally grounded explainability to extracted imaging features; corresponding inverse models can then be endowed with physically plausible structural constraints, as shown for chemical exchange saturation transfer MRI (table).²⁹

Digital neuropathology

Digital neuropathology aims to semi-automate manual histological or immunohistochemical assessment, including precision diagnosis, molecular characterisation, and neuropathological workflow optimisation. Deep learning-based digital pathology trained on whole-slide images has shown utility across various standard diagnostic tasks, including tumour localisation, segmentation, grading, and molecular classification,^{34,36,38,39} with the area under the receiver operating characteristic curve (AUC) often exceeding 0.9 (table). As neuropathological assessments cannot exhaustively inform molecular diagnosis, translational inference can enable spatially resolved profiling via inference of histomolecular tissue properties from standard whole-slide images, such as patch-wise prediction of glioblastoma transcriptional subtypes, revealing survival-related regional gene expression programmes.³⁵

Besides biopsy-based precision diagnosis, rapid molecular diagnosis is paramount for guiding the resective risk-benefit strategy. Stimulated Raman histology^{30,36} (table) or nanopore methylation sequencing data⁴⁰ enable deep

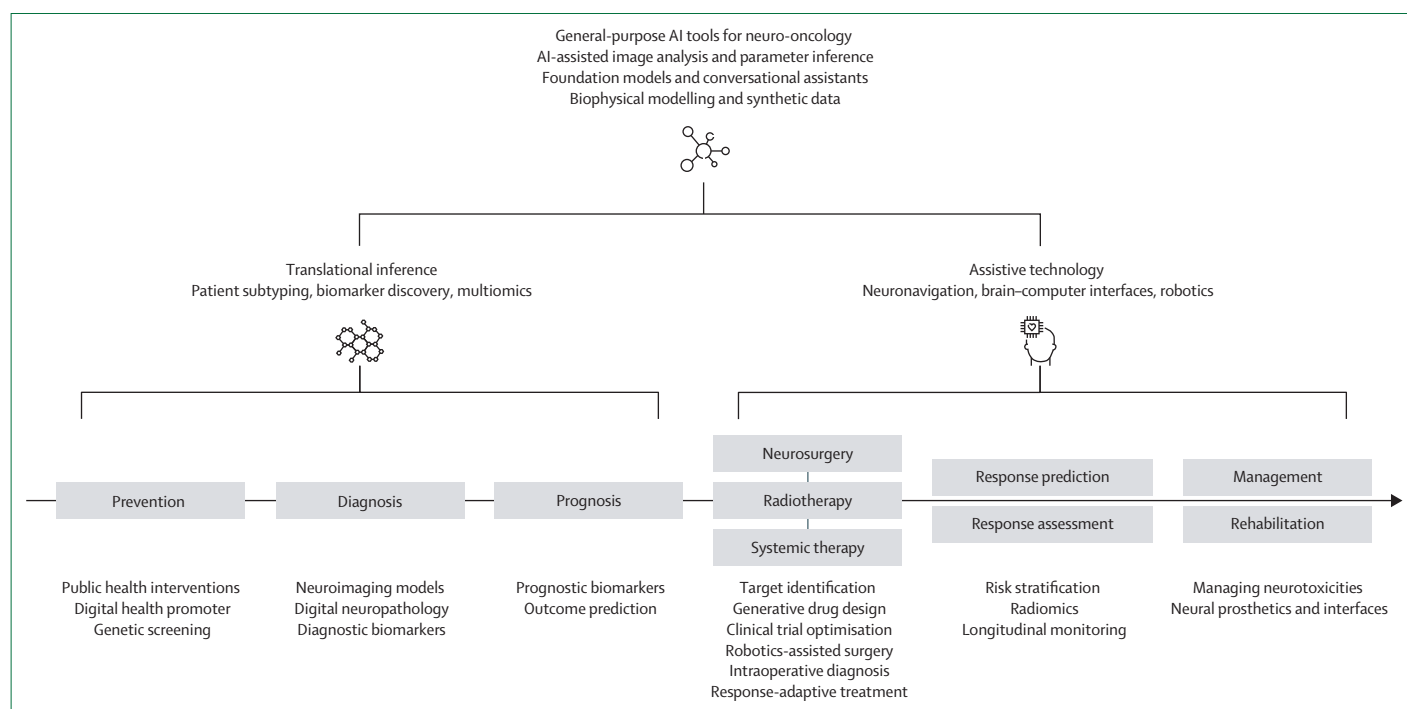


Figure 1: Mapping key machine learning-based technologies along the neuro-oncological care trajectory. AI=artificial intelligence.

learning-based rapid molecular classification, assisting neurosurgeons with intraoperative tumour margin assessment and epigenetic subtyping.

Neuropathological evaluation is often complicated by ambiguous presentation of treatment-related adverse effects (eg, pseudoprogression and tissue necrosis). Although AI-assisted tools can augment diagnostic certainty in ambivalent cases, lack of consensus definitions and reference standards, sampling bias, and frequent presence of mixed lesions (containing both tumour cells or foci and treatment-related pathology) remain principal barriers.⁴¹

Despite considerable potential for automating arduous histopathological tasks or enhancing diagnostic consistency and granularity, neuropathological datasets are typically too large for cost-effective digitisation, storage, and manual labelling; even if digitised and annotated, general applicability of these datasets remains limited by differences in acquisition protocols across institutions and high inter-rater variability. Hence, neuropathology might broadly benefit from the development of foundation models—deep neural networks that are pretrained task agnostically on vast datasets in a weakly or self-supervised manner and consecutively adaptable to specific downstream tasks (panel 2). Although not yet validated in the context of autolabelling pipelines, a prospective multicentre clinical trial showed that a foundation model trained on annotation-free stimulated Raman histology images was superior compared with standard-of-care surgical adjuncts in identifying glioma infiltration during surgery.³⁶ Despite encouraging preliminary results, pervasive foundation model adoption is limited by

prohibitive resource requirements and ethical and regulatory hurdles.

Molecular-genetic tumour characterisation

Most CNS neoplasms are characterised by high histomolecular intertumoural and intratumoural heterogeneity. Molecular data analysis is fraught with difficulties, including high data dimensionality, presence of confounders, and non-linear higher-order interactions between molecular covariates,⁴² implicating some AI techniques as viable alternatives to more classic statistical approaches, whenever appropriate. The data-type agnosticism (panel 1) of AI enables the prediction of molecular modalities, for instance, predicting transcription factor binding affinity for the identification of modulatory single nucleotide polymorphisms⁴² or inferring major genetic alterations (isocitrate dehydrogenase, TERT promoter, and *ATRX* mutation status, and 1p/19q co-deletion status) from global DNA methylation levels in gliomas, with prediction accuracies exceeding 0.9.⁴³

Beyond molecular alterations, concomitant systemic effects of CNS tumours on the nervous system (local tissue innervation changes and modulatory effects on tumour phenotype, facilitating or enabling hallmark capability acquisition)⁸ suggest that particular tumour subtype characteristics manifest in differential connectivity and electrophysiological profiles (both ipsilesionally and contralaterally).^{31,37,44} Indeed, experimental brain metastasis models show atypical calcium-dependent activity in the tumour microenvironment and differentially expressed

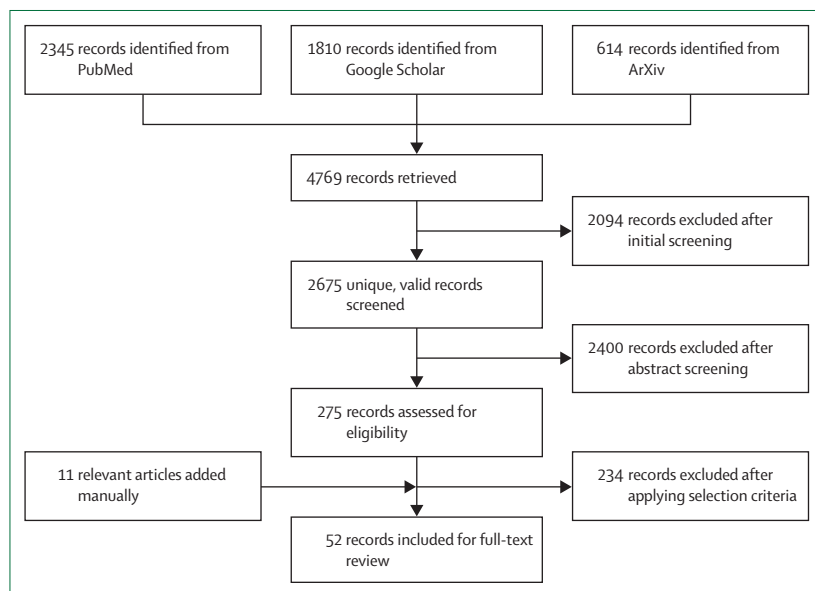


Figure 2: PRISMA flow diagram

genetic profiles, suggesting a delicate interplay of molecular programmes and neural activity patterns (table).³¹ These insights showcase the potential for AI-based activity or connectivity fingerprinting in identifying novel biomarkers and associated precision treatments. The integration of electrophysiological and connectomic characteristics of tumours and affected neural structures derived from intraoperative electrocorticography or magnetoencephalography—shown to be prognostic in glioblastoma^{37,45}—might inform future neural activity-based risk stratification.

Neuro-oncological treatment

Treatment administration

Resection followed by radiotherapy and chemotherapy is recommended for the therapeutic management of most malignant and several benign CNS tumours.³ All approaches fundamentally rely on imaging and digital data processing to delineate the therapeutic target (panel 3). These approaches primarily include radiation treatment planning and delivery.⁴⁸ In recent years, AI-based segmentation models have been implemented in routine clinical practice to delineate healthy anatomical structures (organs at risk) and avoid their exposure to radiation. Ongoing research aims to apply AI for delineation of tumour target structures, including gliomas and brain metastases.⁴⁹ In morphologically straightforward instances without considerable anatomical distortion or alteration from previous treatments, these approaches might improve workflow efficiency, allowing for greater consistency and quality in routine practice or clinical trials. However, standardisation of AI algorithm development and imaging input in defining all biologically relevant regions for treatment, especially for patients with infiltrative malignant gliomas, remains an unmet need.⁵⁰ This challenge also has implications for

surgical approaches, as removal of the tumour portion beyond the contrast-enhancing core has been associated with increased survival in patients with glioblastoma.⁵¹ Nevertheless, distinguishing non-enhancing tumour from oedema with only scattered tumour cells remains a salient discussion point.⁴ Advanced imaging with AI-assisted analysis can eventually guide resection extent by predicting tumour extent beyond contrast enhancement on preoperative imaging.

AI-assisted imaging guidance is already being used in the operating room, with feedback systems analysing operative video in real time.⁵² Such analyses might eventually provide haptic or acoustic feedback on tissue areas with a higher likelihood of harbouring tumour, interpret signals from outside the immediate surgical field (eg, fluorescent signals from tumour remnants or electrophysiological monitoring), or yield early warnings when unnecessarily risky steps are taken. Based on label-free optical imaging methods or methylation profiles, deep neural networks have also been used to intraoperatively diagnose molecular glioma subtypes, further guiding the resective risk–benefit strategy (table).^{30,40} Optimal imaging methods preserving the cytoarchitecture can detect tumour cells in morphologically unremarkable brain parenchyma in real time, enabling tailored resection according to the intraoperative (tissue-based) delineation of the expansive tumour. Further reducing the margin for human error in a high-stress clinical environment, robotic systems performing stereotactic sampling, image-guided microsurgery, or placement of spinal hardware have been shown to be non-inferior to conventional techniques.^{53,54} The role of AI in radiation treatment planning has also been investigated for stereotactic radiosurgery and conventionally fractionated external beam radiation therapy. To date, these studies report variable feasibility and clinical acceptability. Incorporation of clinical outcomes, including tumour control, toxicity, and functional neurological status, should be emphasised in prospective studies of AI implementation.

Systemic treatment and therapeutic target identification

Although delaying of tumour progression is achievable, curative treatment options remain elusive for high-grade adult-type diffuse gliomas; glioblastoma and H3 K27M-altered diffuse midline gliomas (DMGs) are largely unresponsive to chemotherapy. Despite many trials, no novel agents have been approved in the past decade, and the utility of targeted agents remains limited to small patient subsets.¹

As few genetic alterations with clinically validated therapeutic implications are known,^{19,55} identification of patient strata responsive to some therapeutic approaches might help to improve patient management towards tailored therapy recommendations. Unsatisfactory outcomes in glioblastoma treatment with immune checkpoint inhibitors (ICIs) have prompted efforts to select ICI-responsive patient subgroups based on glioblastoma stemness using AI-based stemness predictors from RNA-seq profiles (table). High-stemness tumours are associated with increased

programmed death-ligand 1 (PD-L1) inhibitor susceptibility, improved overall survival, greater genomic instability, and distinct tumour immune microenvironment profiles.³³ AI-based prediction of single-sample gene enrichment analysis scores of selected signatures along histomorphologic glioblastoma niches and subsequent clustering identified a proteomic MYC–KRAS–hypoxia programme promoting intratumoral heterogeneity. The axes correlate with aggressiveness, differential drug sensitivities, and relative chemoresistance.⁵⁶ Notably, pharmacological drug sensitivities were explained better by these protein-defined axes than by established transcriptional subtypes, implicating immune checkpoint protein CD276 (vasculature) as a potential ICI target rather than PD-L1.⁵⁶ A cross-type proteogenomic study comparing low-grade glioma and glioblastoma identified IDH1 and EGFR to be mutationally exclusive and highlighted tumour type-specific kinase preference, signalling the potential targets in differentially enriched pathways.⁵⁷

Despite vast numbers of suggested druggable targets, their respective roles in contributing to phenotypic tumour variations remain unclear. Identification of nexus molecules orchestrating these phenotypic variations is pivotal.³² Studies have shown the utility of AI in inferring kinase–substrate phosphosite interactomes³² in glioblastoma, leading to the identification of highly active master kinases³² in functional glycolytic or plurimetabolic subtypes, and in proliferative or progenitor glioblastoma subtypes (table).³² To inform patient allocation for prospective clinical trials, functional glioblastoma subtypes were predicted using RNA-seq data from frozen tissue samples (AUC >0.83 for all classes).³² Target identification, in combination with AI-driven de novo compound design, could profoundly accelerate the development of novel therapies. However, as the first drugs developed using AI are only now entering clinical trials, their effectiveness remains to be confirmed (appendix p 3).

A plethora of other therapeutic avenues is on the horizon,⁵ including, but not limited to, novel immunotherapies, chimeric antigen receptor T cells, oncolytic virotherapy, multimodal combination therapies, optimised therapy sequencing, and drugs targeting neural–cancer cross-talk and nervous system cancer networks.⁷ Clinical trials on tumour network disconnection strategies targeting gap junctions in glioblastoma and inhibition of glutamatergic neuron-to-glioma synapses are ongoing,⁷ warranting investigations into AI-assisted identification of structural and molecular drivers of nervous system cancer network function, novel biological agents, and the utility of electrophysiological or neural signalling biomarkers.

Prognostication, response prediction, and assessment

Molecular-genetic risk stratification and prognosis

In addition to general clinical prognostic factors such as age and clinical status, tumour-specific risk stratification is primarily guided by histomolecular characteristics (eg, MGMT promotor methylation status and H3K27M mutation in

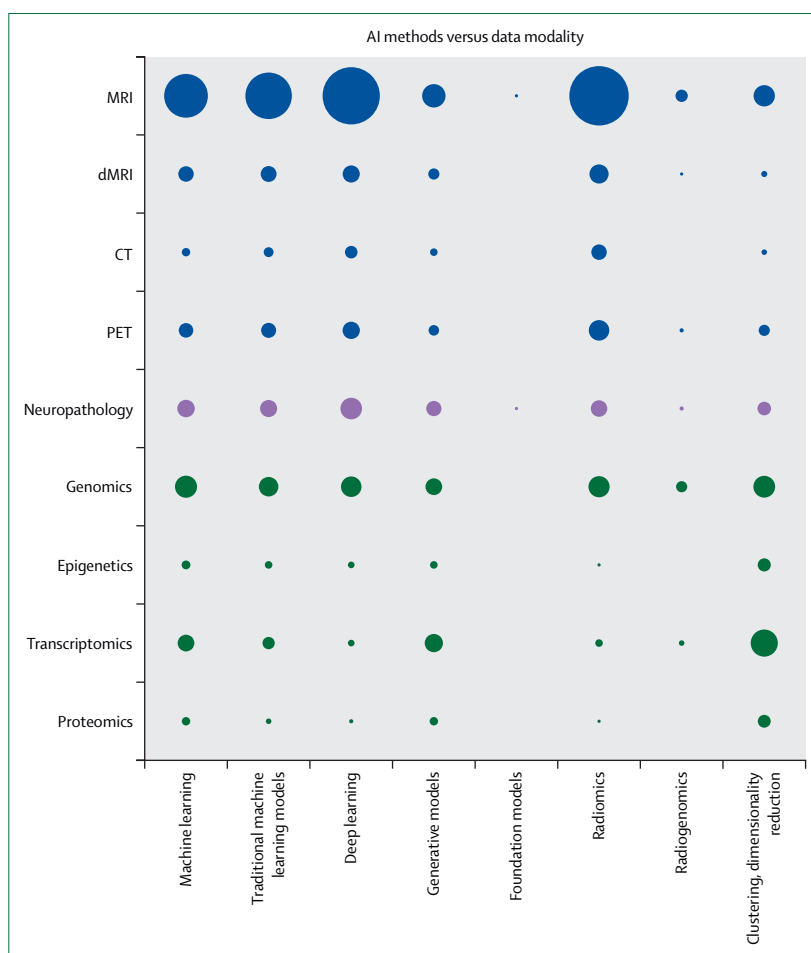


Figure 3: Distribution of machine learning methods (x-axis) per neuro-oncological data type (y-axis)

The circle size is proportional to the number of abstracts referencing method-data-type pairs in the 2675 filtered articles. Our search revealed that the current literature is largely dominated by studies on clinical imaging and radiomics as well as deep learning and classic statistical methods, which are also prominently used for omics studies; few studies have investigated niche modalities and advanced techniques. Raw data are provided in the appendix (p 4). Blue indicates clinical imaging, purple indicates neuropathology, and green indicates omics. AI=artificial intelligence. dMRI=diffusion MRI.

DMGs). Translational inference from structural MRI and diffusion tensor imaging can improve outcome predictions, such as overall survival and progression-free survival, and has been linked to risk score-specific differentially enriched pathways and histomolecular signatures.^{24,25,37}

However, current stratification schemes often do not capture the relevant morphometric, epigenetic, and transcriptomic tumoural intragroup heterogeneity, warranting efforts to refine established imaging-derived or molecular-genetic strata.^{35,58–63} For example, AI-derived cytoarchitectonic features from whole-slide images in low-grade gliomas correlate with overall survival, revealing poor prognosis subtypes characterised by high mutational load, frequent copy-number alterations, and substantial tumour-infiltrating lymphocyte presence.⁵⁹ In some tumour entities, such as high-grade astrocytoma with piloid features (HGAP), morphometric subclasses alone offer limited

Panel 1: A primer on machine learning for neuro-oncologists and allied health professionals

ML is a subdiscipline of AI, although the two terms are used quasi-synonymously. ML is the data-driven optimisation of (parametric) functions with respect to predefined optimisation objectives. A plethora of ML techniques are used across neuro-oncology, with selected techniques becoming part of the standard armamentarium of a neuro-oncological AI researcher or practitioner.

Clinical imaging-based AI studies are dominated by DNNs and radiomics. DNNs are universal function approximators, ie, they can, in principle, approximate arbitrarily complicated piecewise continuous non-linear mappings, provided sufficient parameters, data, and computational resources are available. This capability is independent of data type, resulting in data and function agnosticism, leading to extreme versatility of DNNs. In practice, DNN optimisation is constrained by various factors beyond resource limitations, and deep learning practitioners have limited control over which dependencies between covariates in the data are learned. However, in most cases, these challenges do not result in obvious errors—ie, DNNs tend to fail silently. The fundamentally data-driven nature of the optimisation results in difficulties in interpreting the outputs of DNNs and estimating how well they can generalise beyond the data they have been optimised (trained) on. Even when an algorithm seems to work on a given validation cohort, a theoretical guarantee that the algorithm will perform comparably on another does not exist, underlining the importance of extensive, multicentre validation studies before introducing AI-based solutions into routine clinical practice. Radiomics is fundamentally different from deep learning because it relies on the extraction of predefined statistical features from images, and subsequent mapping of selected features to a desired target variable (sometimes using DNNs after feature extraction). Predefining and selecting features can, but does not ubiquitously, improve performance, potentially warranting a balanced side-by-side evaluation of purely deep learning-based and radiomics feature extraction.

In contrast to imaging-based studies, histomolecular and multiomics studies tend to integrate various ML techniques at key steps of extensive data analysis pipelines, which are often equally populated by classic statistical and specialised bioinformatics techniques. As opposed to most ML methods, these techniques can have strong biological priors and might only be applicable to specific data or problem types. ML is often used when classic statistical approaches face difficulties owing to high data dimensionality, the presence of many confounders, non-linear interactions between covariates, and unknown functional relations between covariates of interest. In analyses with thousands of covariates, the sample sizes needed to control for spurious correlations with statistical techniques are exceedingly large. Clustering and dimensionality reduction techniques have become standard tools in a bioinformatician's repertoire to discover low-dimensional structures in high-dimensional data. Clustering identifies groups of data points that are close to each other based on a user-defined distance metric, while dimensionality reduction maps high-dimensional data points to a low-dimensional space, such that the information retained in the latent encodings captures an aspect of interest that is not visible in the high-dimensional representation. Linking molecular layers by predicting potentially non-linear interactions between covariates is often framed as an ML problem. ML models can use spurious correlations in the data for predictions, necessitating the explicit modelling of confounders using biological or structural priors to guide optimisation—an area of active research.¹¹

AI=artificial intelligence. DNN=deep neural network. ML=machine learning.

utility because intragroup differences evade standard assessment. Nonetheless, hierarchical clustering of epigenetic profiles in HGAP reveals clinically salient subtypes, such as a neurofibromatosis type 1-mutated hypermethylated HGAP subtype with reduced tumour purity and poor progression-free survival.⁶⁰ Beyond HGAP, clustering and dimensionality reduction approaches (panel 1) delineate distinct epigenetic subclasses in DMGs and glioblastomas,^{60–62} characterised by atypical histomolecular features and differential clinical outcomes. For instance, H3.3K27M-mutated DMGs tend to have poor overall survival and are unresponsive to chemotherapy,¹ whereas H3.3K27M tumours with *BRAF* or *FGFR1* co-mutations form a distinct epigenetic–transcriptomic cluster with divergent histology and slightly favourable prognosis.⁶² Glioblastoma further shows how transcriptional difference can complicate prognosis; the transcriptomic high-neural subtype shows hypomethylated CpG sites and upregulation of genes associated with synaptic integration, fostering neuron-to-glioma synapse formation negatively associated with overall survival and progression-free survival (table).³⁷ This transcriptional heterogeneity is a key driver of therapy resistance in glioblastoma, as the co-existence of transcriptional niches hinders effective targeting of subtype-specific molecular alterations.⁶⁴ Mapping these regional gene expression programmes to tumour morphology,

connectivity, and signalling in turn opens the door for AI-driven identification of novel biomarkers in magnetoencephalography, digital pathology, or blood serum—enabling a spatially resolved understanding of molecular programmes in glioblastoma (table).^{35,37} Ultimately, synergies between clinical imaging, deep molecular profiling, and AI-powered stratification might foster the discovery of novel prognostic biomarkers and associated tumour subgroups, providing guidance for more personalised prognostication and therapeutic management, including targeted subgroup-specific interventions.

Response prediction and assessment

Sequential, rigorous, and methodical review of imaging in neuro-oncology is essential for treatment decisions, response assessments, and distinguishing treatment-related adverse effects (eg, pseudoprogression, tissue necrosis) from tumour progression. AI-assisted tumour volume quantification in structural MRI has shown a substantial reduction in inter-rater variability of estimated time to progression (table)¹⁸ and increased reliability in detecting pseudoprogression in high-grade gliomas.⁶⁵ Similarly, co-registered spherical-projected contrast-enhanced structural MRI integrated with dose maps enabled the prediction of local control outcomes for brain metastasis following stereotactic radiosurgery (AUC 0.89).⁶⁶

	Objective	Resources	Methods and results
Hollon et al (2023) ³⁰	Intraoperative diagnosis via SRH-based prediction of molecular features in diffuse gliomas	Endpoints: molecular classification accuracy, F1 score Data: whole-slide SRH images of fresh, unprocessed gliomas of 373 patients with adult-type glioma; public glioma genetic data of 2777 patients from six resources (training) and 153 patients with diffuse glioma (testing) Study type: retrospective multicentre study	Image and genetic encoder training: CNN vision encoder pretrained on multilabel supervised contrastive loss Genetic alteration prediction: transformer pretrained on vision and genetic embeddings for prediction of masked genetic alterations Molecular classification: accuracy of 0.947 (IDH), 0.941 (1p19q co-deletion), and 0.910 (ATRX); F1 scores of 0.963 (IDH), 0.966 (1p19q co-deletion), and 0.947 (ATRX) Direct classification of SRH images into three WHO CNS5 classes: overall subgroup classification accuracy was 0.915; accuracy in patients 55 years or younger was 0.944
Sanchez-Aguilera et al (2023) ³¹	Characterisation of brain metastasis subtypes via differential neural activity modulation signatures	Endpoints: metastasis type prediction accuracy Data: electrophysiologically recorded neural activity (LFPs from all groups recorded at 7 and 10 days postimplantation) and categorical features from three organotropic mouse brain cancer cell lines (482N1-BrM, E0771-BrM, B16/F10-BrM) and one control Study type: prospective, single-centre study	Effect of brain metastasis on neural activity: reduced cortical and hippocampal activity ipsilateral to metastasis across all frequency bands; contralateral effects only in 482N1-BrM; activity differences not reflecting locomotor activity or volume conduction effects; LFP differences not explained by mass effect or peritumoural inflammatory milieu; correlation between metastasis type and transcriptomic programme Metastasis type predicted using decision tree: PCA used for projection of features on linear subspace; decision tree used for metastasis-type prediction 9–10 days after injection with a mean accuracy of 0.77 (SD 0.02) and 7 days after injection with a mean accuracy of 0.73 (SD= 0.09)
Vollmuth et al (2023) ¹⁸	Assessment of AI-based volumetric tumour burden quantification to improve standardisation and reliability of response assessment between evaluators compared with standard RANO criteria	Endpoints: concordance correlation coefficient for time to progression Data: 3D T1w, 3D cT1w, 2D axial FLAIR, 2D axial T2w, DWI with ADC maps from two imaging timepoints from 30 patients with diffuse glioma Study type: retrospective multicentre study	Performance improvement owing to AI-based decision support: CNN for computational skull stripping and tumour segmentation; concordance between raters increased from 0.77 (95% CI 0.69–0.88) (RANO-based) to 0.91 (95% CI 0.82–0.95) (AI-assisted). The effect was more pronounced for lower-grade glioma (CCC 0.70 to 0.90) than for glioblastoma (CCC 0.83 to 0.86). The inter-rater agreement on time to progression increased in terms of standard deviation (ie, the SD decreased); evaluators with less years of experience rated the AI-based decision support as more helpful than those with more years of experience.
Perlman et al (2022) ²⁹	Utilisation of simulated CEST MR fingerprinting for training a deep neural network to detect and quantify apoptotic response to oncolytic virotherapy	Endpoints: not applicable Data: CEST MRI 8–11 days after tumour implantation, 48 and 72 h after oncolytic virotherapy treatment in U87ΔEGFR human glioblastoma orthotopic mouse model and one healthy human control Study type: prospective, single-centre study	Simulated CEST magnetic resonance fingerprinting and model training: numerical simulation of expected signals for 70 million tissue parameter combinations (T1, T2, B0 inhomogeneities, and four semisolid, amide chemical-exchange parameters) for two acquisition protocols Tissue parameter inference from simulated fingerprints: two small densely connected deep neural networks trained to consecutively extract four chemical-exchange parameters from given simulated MRI Treatment response monitoring: quantitative response maps from mouse models were compared at the three different measurement timepoints; all signals were substantially altered in the tumour after OV inoculation (the first three decreased; only the tumour amide proton exchange rate increased), which indicated reduced pH and protein concentration, suggesting apoptosis Tissue-based validation of molecular findings: histological stains (H&E, Coomassie) and immunohistochemistry images (HSV, Caspase-3) were used to verify response maps Validation in healthy human controls: after adaptation to a clinical 3 T MRI scanner, all maps were in agreement with those reported in previous studies
Migliozzi et al (2023) ³²	Therapeutic target identification via multiomics characterisation of glioblastoma; discovery of master kinases orchestrating phenotypic hallmark acquisition in glioblastoma functional niches	Endpoints: glioblastoma subtype prediction AUC Data: genetic, epigenetic, transcriptomic, proteogenomic, metabolomic, lipidomic, and phosphoproteomic data from 92 patients with IDH wild-type glioblastoma from CPTAC and 282 patients with IDH wild-type glioblastoma from TCGA Study type: retrospective, multicentre study	Functional glioblastoma subtype discovery: <i>k</i> -nearest neighbours classifier trained on gene expression profiles uncovered four functional glioblastoma subtypes Kinase-substrate phosphosite interactome inference: ensemble of support vector machine classifiers trained on known substrate-kinase pairs for interactome construction and model-based kinase activity prediction identified PKCδ and DNA-PKcs master kinases in the functional glycolytic or plurimetabolic subtypes as well as in proliferative or progenitor glioblastoma subtypes BJE6-106 (PKCδ inhibitor) and nedisertib (DNA-activated protein kinase inhibitor) were suggested as potential targeted agents Probabilistic IDH-wildtype glioblastoma prediction: multinomial regression model with lasso penalty trained on RNA-seq to predict functional glioblastoma subtype (AUC 0.83)
Wang et al (2021) ³³	Introduction and clinical validation of a novel stemness-based classification as prognostic predictors for glioblastoma; utilisation of multiomics analysis to reveal targetable pathways; patient stratification to identify glioblastoma cohorts responsive to ICIs	Endpoints: stemness subtype predictor accuracy, sensitivity, specificity, AUC Data: predicted mRNA stemness index-associated differentially expressed genes for two stemness subtypes that were found via clustering and annotation (literature) and clinical patient status from 868 patients with glioblastoma from two databases (training and validation); 388 patients with glioblastoma from one database and one institute (testing) Study type: retrospective, multicentre study	mRNAsi annotations: mRNAsi was negatively correlated with immune infiltration levels, not correlated with tumour purity, positively correlated with T-cell subsets, and negatively correlated with macrophage abundance; high mRNAsi was associated with better OS (HR 0.80) and poorer PFS (HR 1.28); mRNAsi was independent of other clinical variables; differential expression analysis revealed 130 DEGs Stemness-based subtyping and annotation: <i>k</i> -means-based consensus clustering revealed two distinct subtypes with different tumour immune microenvironments, immunogenomic patterns (subtype 1 had higher CNA and mutation burden and was more sensitive to immunotherapy but resistant to TMZ), and clinical variables (eg, young patients with subtype 1) Identification of subtype-specific compounds: DEGs between subtypes and pathway annotation revealed 34 potential compounds for type 1 and 76 potential compounds for type 2 ML-based stemness predictor: (1) four different classifiers trained on stemness-associated DEGs to predict the status of stemness subtype; (2) intersecting highly predictive genes identified; (3) final multivariate logistic regression classifier trained on these genes to predict status, resulting in AUC of 0.96, accuracy of 0.93, sensitivity of 0.91, and specificity of 0.94

(Table continues on next page)

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Objective	Resources	Methods and results
(Continued from previous page)		
Wang et al (2023) ³⁴	Digital pathology-based molecular glioma diagnosis from annotation-free WSIs	Endpoints: diagnostic AUC Data: H&E WSIs and diagnostic class label of 1702 patients with diffuse glioma from one institute, and 922 patients with diffuse glioma from three institutes Study type: retrospective, multicentre study
Zheng et al (2023) ³⁵	Utilisation of spatial transcriptomics and deep learning to map WSIs to glioblastoma transcriptional subtypes; linking transcriptional subtype to clinical outcomes; uncovering OS-related regional gene expression programmes	Endpoints: transcriptomic subtype prediction AUC Data: 75 625 transcriptomic spots and 69 647 H&E WSI patches from 22 patients with glioblastoma from three public sources, and an additional eight patients and 312 patients with glioblastoma from two public sources (training and validation); 98 patients with glioblastoma from one public source (testing) Study type: retrospective, multicentre study
Kondepudi et al (2025) ³⁶	Fast and accurate detection of glioma infiltration in fresh, unprocessed surgical tissues using a vision FM	Endpoints: degree of infiltration (mean AUC, MAE) Data: 11 462 whole-slide SRH images of fresh, unprocessed surgical specimens of 2799 patients with adult-type glioma (pretraining); 3560 whole-slide SRH images from 896 patients (testing); 767 IDH-mutant and 659 IDH-wild-type diffuse gliomas resulting in 1130 total specimens (prospective clinical trial for testing) Study type: prospective international multicentre single-arm, non-inferiority, diagnostic clinical trial
Drexler et al (2024) ³⁷	Definition of epigenetically defined neural signatures from transcriptomic profiles; linking signatures to OS and PFS; characterisation and potential biomarker identification	Endpoints: OS, PFS, functional connectivity in glioblastoma; stability of epigenetic neural classification Data: multicohort, multiomics profiles (DNA methylation, transcriptomics, proteomics, spatial transcriptomics) of 5047 CNS tumours (including 1058 patients with glioblastoma from combined cohorts and 187 from TCGA), additional single-cell and patient-derived xenograft datasets, and a validation set of 72 diffuse midline gliomas Study type: retrospective, multicentre study
Consensus was reached among all co-authors to select papers for their emphasis on common pathologies, clinical relevance, methodological rigour, novelty, and potential impact on neuro-oncological practice and research. 3D=3-dimensional. 2D=2-dimensional. ADC=apparent diffusion coefficient. AI=artificial intelligence. ALA=aminolevulinic acid. AUC=area under the receiver operating characteristic curve. BDNF=brain-derived neurotrophic factor. CCC=concordance correlation coefficient. CEST=chemical exchange saturation transfer. CNA=copy number alteration. CNN=convolutional neural network. CPTAC=Clinical Proteomic Tumor Analysis Consortium. cT1w=contrast-enhanced T1-weighted MRI. DEG=differentially expressed gene. DWI=diffusion-weighted imaging. FLAIR=fluid-attenuated inversion recovery. FM=foundation model. fMRI=functional MRI. H&E=haematoxylin and eosin. HR=hazard ratio. HSV=Herpes simplex virus. ICI=immune checkpoint inhibitor. IDH=isocitrate dehydrogenase. LFP=local field potential. MAE=mean absolute error. MEG=magnetoencephalography. ML=machine learning. mRNAsi=messenger RNA stemness index. NMF=non-negative matrix factorisation. OS=overall survival. OV=oncolytic virotherapy. PCA=principal component analysis. PFS=progression-free survival. RANO=response assessment in neuro-oncology. SRH=stimulated Raman histology. T1w=T1-weighted MRI. T2w=T2-weighted MRI. TCGA=The Cancer Genome Atlas. TMZ=temozolomide. WSI=whole-slide image.		
Table: A selection of ten high-impact publications that highlight use cases of machine learning in different areas of neuro-oncology		

Panel 2: Generalist foundation models in neuro-oncology

Foundation models are DNNs that undergo weak or self-supervised pretraining on large-scale, possibly multimodal datasets (containing up to trillions of samples); they can flexibly adapt to a diverse set of downstream tasks, either by supervised training on much smaller annotated datasets (fine tuning), or novel training schemes, such as instruction fine tuning via natural language instructions. After (instruction) fine tuning, foundation models can adapt to novel tasks using only examples or instructions (in-context learning).^{9,10} Such capabilities suggest a potential role of foundation model-based medical AI systems with truly generalist functionality. These systems can assist clinicians across a broad spectrum of clinically relevant tasks, including medical question answering, image classification, radiology report generation and summarisation, and genomic variant calling. Generalist foundation model-based assistants could, for example, suggest diagnoses, integrating molecular data into its considerations, provide recommendations informed by the most recent literature and clinical trial data, assist in the operating room by delineating tumour boundaries, recommend personalised treatments, and offer a prognosis based on the data collected at all previous steps, enabling human–AI collaboration.^{9,10} Beyond their role as conversational or agentic assistants, neuro-oncological foundation models can integrate non-human interpretable data, such as molecular or neural activity data, directly into their training without encoding the data as natural language first, augmenting human capabilities rather than simply acting as assistant technology. Foundation models are yet to be validated in real-world clinical contexts. The key challenges include limited reliability, misalignment with human intent and values, unquantifiable extrapolation capabilities, privacy concerns related to potential reproduction of sensitive patient information, and the requirement for very large training datasets alongside vast computational resources.

AI=artificial intelligence. DNN=deep neural network.

An exciting frontier accompanying advances in treatment delivery is the development of novel imaging platforms for the iterative evaluation of tumour status throughout the course of conventional radiotherapy. An improved understanding of the biological relevance of changes observed during the course of radiotherapy might enable a shift from rigid treatment paradigms towards response-adaptive radiotherapy, allowing responsiveness to emerging treatment resistance during the course of radiotherapy and improving the therapeutic ratio.⁶⁷ Similar approaches have been applied to imaging-based disease monitoring of patients with glioblastoma during post-radiation medical treatment, with the depth and duration of response serving as predictors for survival in glioblastoma.⁶⁸

However, substantial intragroup outcome heterogeneity in large classes of CNS neoplasms is not yet reflected in clinical management recommendations. AI-based therapy response prediction might enable more granular risk and sensitivity stratification, as shown for various entities and therapies.^{29,33,55,69,70} Transcriptomic analyses of the glioblastoma tumour immune microenvironment suggest the utility of risk stratification and therapy response prediction based on an AI-predicted stemness index³³ and immune cell-associated long non-coding RNA.⁶⁹ Glioblastoma groups organised along the stemness axis, inferred and predicted from gene expression data (AUC 0.96), are characterised by a distinct mutational burden, tumour immune microenvironment profiles, and immunogenomic patterns, as well as differential sensitivity to ICIs (table).³³ Radiomics or radiogenomics was used for response prediction to targeted therapies (eg, dabrafenib plus trametinib in BRAF^{V600E} mutant gliomas)⁵⁵ for low-grade and high-grade glioma and ICI therapy (eg, predicting PD-L1 expression levels), as shown in a study on molecular brain metastasis profiling from structural MRI.⁷⁰ Notably, simulated chemical exchange saturation transfer magnetic resonance fingerprint images have been used to monitor apoptosis as an early predictor of treatment response to oncolytic virotherapy; a deep neural network could infer metabolic changes from quantitative maps of chemical-exchange parameters in

a glioblastoma orthotopic mouse model (table).²⁹ However, whether changes in novel response parameters are clinically meaningful warrants rigorous validation of clinical effectiveness, *inter alia*, to mitigate overinterpretation.

Management and rehabilitation

Tumour-related and treatment-related complications

Management of tumour-related and treatment-related adverse effects represents a growing neuro-oncological challenge, given the recent improvements in cancer survivorship, particularly for patients with brain metastases. The nature and burden of potential toxicities have substantially evolved with the increased utilisation of stereotactic radiosurgery and adjuvant integration of targeted therapies.⁶³ Late CNS toxicities include cognitive dysfunction, leukoencephalopathy, brain atrophy, cerebrovascular complications, endocrinopathies, and brain tissue necrosis.^{63,71} Differential spatial radiographic patterns provide an opportunity for AI-assisted monitoring of treatment-induced tissue necrosis to circumvent unnecessary exposure to antineoplastic therapies or treatments that undermine the effectiveness of systemic therapies. To elucidate the molecular correlates of radiotoxicity, AI can be used to predict radiotoxicity-associated gene expression signatures that correlate with overall survival in glioblastoma.⁷² Efforts to prevent or mitigate CNS radiotoxicity are imperative. AI can improve radiation field planning to spare proximal organs at risk and facilitate the development of reliable non-invasive surveillance platforms for risk stratification, early detection, and effective management of treatment-related toxicities (appendix p 3).

Neurocognitive and motor rehabilitation

Tumour-related complications or adverse effects can be progressive and irreversible, resulting in cognitive impairment and permanent neurological disability, diminishing quality of life and even affecting survival.⁷¹ AI-assisted neurocognitive rehabilitation has shown promising results in individuals with paralysis and associated speech and motor deficits. Existing approaches include

Panel 3: Selected applications and associated key considerations for medical AI in neuro-oncology stratified by regulatory stage

Available with FDA 510(k) or equivalent regulatory clearance

Listed applications and publications were selected for didactic purposes, emphasising clinical relevance, novelty, proof of principle, and potential effect on neuro-oncological practice and research. Applications with 510(k) clearance were identified by searching the FDA AI or machine learning-enabled medical devices list for relevant FDA-approved AI-based medical devices (up until Jan 26, 2025).⁴⁶

Applications

- Automated visualisation, segmentation, registration, volumetric quantification, and labelling of brain structures from magnetic resonance images for diagnosis and radiotherapy planning (eg, TeraRecon Neuro [TeraRecon, USA, 2022], ClearPoint Maestro Brain Model [ClearPoint Neuro, USA, 2022], NS-HGlio [Neosoma, USA, 2022], VBrain [Vysioneer, USA, 2021] NeuroQuant [CorTechs Labs, USA, 2017])
- Noise reduction in magnetic resonance images (eg, SubtleMR [Subtle Medical, USA, 2023])
- Generation, visualisation, and evaluation of pseudo-CT from magnetic resonance images (eg, ART-Plan [TheraPanacea, France, 2023])

Barriers to clinical implementation

Disconnect between research and approval of medical devices or utilisation in routine clinical practice:

- Data gap: lack of high-quality, annotated, centralised, anonymised, diverse, representative data for model development
- Validation gap: lack of international, multicentre, prospective trials to show clinical viability of novel methods, accounting for potential transfer penalty or performance deterioration over time
- Implementation gap: disconnect between approval of medical device and active clinical use; successful reimbursement or financial viability often not guaranteed or achieved despite approval; demonstration of improved outcomes crucial to success beyond formal approval

Clear pathway to regulatory approval and commercialisation

Applications

- Identification, location, and characterisation of suspicious area(s) on digitised whole-slide images (eg, Paige Prostate [Paige.AI, USA, 2020]): approved in the context of prostate tumour detection, feasibly transferable to neuro-oncological use cases
- Foundation model-based application fine-tuned to specific use cases (eg, based on Health Developer Foundation⁴⁷)

Barriers to clinical implementation

- Difficult or unclear recertification for improved models or different application of existing models
- Licensing issues in the context of open-sourced models developed in research contexts (eg, foundation models); patentability of novel models developed on top of open-source model or method

Unclear pathway to regulatory approval or commercialisation

Applications

- Generalist, promptable models capable of zero-shot generalisation in novel contexts^{3,36}
- Generative models for synthetic data generation²⁹

Barriers to clinical implementation

- Need for novel regulatory frameworks for novel technologies (eg, foundation models or biophysical models that ensure safety, equity, and bias minimisation in models with strong zero-shot generalisation abilities or trained to learn in-context)
- Recertification infeasible for each new use case
- Need for standardised protocols, prospective validation, and a shift towards federated learning to enable large, decentralised collaborations across institutions

AI=artificial intelligence. FDA=Food and Drug Administration.

intracortical brain–computer interfaces (BCIs) to decode attempted handwriting movements from motor cortex activity,⁷³ subdural multielectrode arrays, and non-invasive interfaces that can translate neural activity into speech.^{11,74} Conversely, it is conceivable that generative models for BCI-mediated or neurostimulation-mediated manipulation of spatiotemporal neural activity could support restoration of complex motor or impaired higher-order neurocognitive functions. Translating these concepts to neuro-oncology can help to optimise brain health through functional restoration, improved communication abilities, enhanced societal participation, and better quality of life, especially in long-term survivors with cancer-related neurocognitive impairments.

Opportunities, pitfalls, and future directions

AI-based decision support systems hold promise to assist clinicians across the entire neuro-oncological care trajectory (panel 4). Selected applications for well circumscribed tasks can augment specialist care^{15,18} and, in some cases, have received regulatory approval (panel 3). Insufficient generalisability, poor reproducibility and data accessibility, absence of consensus definitions and reference standards for validation, ethico-legal issues, and regulatory hurdles remain principal barriers to their broad applicability.⁴¹

Here, we highlight the progress in promising emerging applications, including foundation model-based neuro-oncological assistants, biophysical modelling, and use of synthetic data for drug discovery and inverse

Panel 4: Clinical challenges in artificial intelligence in neuro-oncology and associated future directions

Discovery of predictors of disease onset and performing preventive risk stratification

- AI-driven integration of genome-wide association study data¹³ with other molecular layers, functional annotation for risk group identification based on molecular profiling (eg, enabling identification of novel mutations or interacting gene modules,⁵⁶ preventive liquid biopsies, or structural MRI for identified risk groups)
- Prevention of metastatic spread via oncogenic driver identification¹⁴
- Prediction of likelihood of treatment-related adverse effects

Reduction of human error and inter-rater variability in diagnosis and treatment response assessment

- Diagnostic neuroradiological assistance via CNS tumour detection, classification, grading, and segmentation, and synthetic data generation^{15,17,75}
- Multimodal models for longitudinal integration of clinico-molecular variables and care trajectory-wide assistance¹⁰

Histomolecular precision diagnosis

- Inference of molecular alterations from non-invasive clinical imaging (MRI, CT, PET, ultrasound) or histological imaging (whole-slide image, cryosections)^{16,20,21,23,30,34,39}
- Annotation of known histomolecular subtypes with differentially enriched pathways
- Discovery of novel histomolecular subtypes^{35,58–62}
- Prediction of relevance of molecular alterations of unknown clinical significance

Personalised or agile treatment planning and delivery

- Radiation therapy planning⁴⁸
- Tumour segmentation, prediction of optimal resection margins, closed-loop surgical guidance systems⁵²
- Real-time intraoperative diagnosis based on ultrasound²⁶ or optical methods³⁰
- Robotics-aided tissue sampling or microsurgery⁵⁴
- Personalised therapy recommendation based on AI-predicted response³³
- Iterative status evaluation, response assessment, and monitoring by imaging-based volumetric assessment,¹⁸ metabolic imaging,²⁹ discrimination of pseudoprogression from true progression,⁶⁵ metastatic invasion, and agile treatment administration

Personalised risk stratification

- Overall survival, progression-free survival, treatment-related adverse effect prediction^{24,33,76}
- Discovery of association between predicted risk score and molecular-genetic traits, such as intratumoral heterogeneity³⁷
- Introduction of novel risk stratification schemes based on immunological or molecular-genetic tumour traits³³
- Adverse event prediction and monitoring to prevent treatment-related complications

Restorative neurorehabilitation

- Non-invasive neural interfaces to mitigate loss of function due to tumour-related or treatment-related neurocognitive sequelae⁷⁴
- Invasive brain-computer interfaces to mitigate or restore loss of sensory, motor, or cognitive function by recording and machine learning-based decoding of neural activity, activity-based control of language interface, or neuroprosthetic devices^{11,73}

Discovery of novel drug targets and biological agents

- Identification of phenotype-associated molecules as potential druggable targets³²
- Generative de novo design of small molecules or proteins with predefined properties⁷⁷ and computational high-throughput testing based on a biophysical model of agent-target interaction

Mechanistic models of disease

- Integrative molecular data analysis^{32,33,57}
- Biophysical or causal models of disease dynamics⁷⁷

AI=artificial intelligence.

problems, and critically examine the challenges related to current data limitations, validation, and implementation gaps.

Foundation model-based neuro-oncology assistants

An increasing interest in foundation models, particularly in digital pathology, signals a shift towards generalist models trained on large-scale, multimodal datasets and adaptable to

varied downstream tasks (panel 2). Using foundation models as a backbone for well delineated applications^{34,36} might constitute a strategy to facilitate their regulatory approval. However, reproducible validation studies and rigorous benchmarking are essential to evaluate foundation model-based applications against high-performing, task-specific models.

Contrastingly, instruction-fine-tuned foundation models might aid practising clinicians across a broad range of

tasks as generalist or agentic neuro-oncological assistants (panel 2) that communicate through natural language interfaces.⁹ However, uncertain zero-shot generalisation capabilities, potential biases, and inadequate alignment hinder the development of pertinent regulatory pathways for clinical adoption. Alongside the development and implementation of foundation model governance guidelines,⁷⁸ technical advancements are required to ensure truthfulness and strict adherence to ethical principles, particularly in safety-critical scenarios. Existing access inequities with respect to data access and AI model access—potentially exacerbated by the vast data and computational requirements of pretraining—require pre-emptive mitigation, prompting efforts to bridge the digital divide by democratising access and enabling local deployment through open-sourcing medical foundation model parameters.⁴⁷

Biomarker discovery, biophysical modelling, and synthetic data

The data-type agnosticism of AI (panel 1) facilitates the identification of preventive, diagnostic, and prognostic biomarkers; inference of histomolecular properties from routinely performed clinical imaging for non-invasive diagnosis or continual monitoring; and risk stratification into known, refined, or novel diagnostic, therapeutic, and prognostic groups.

However, if data are scarce or possess an inherent domain-specific structure, this domain agnosticism can hinder convergence towards satisfactory solutions. To address this limitation, deep neural networks can be endowed with inductive biases that encode domain-inherent causal, relational, or semantic structures (eg, symmetries, intrinsic dimensionality, biophysical, geometric, or relational priors, and probabilistic or causal structures).⁷⁷ Relational priors can support drug target identification and spatial transcriptomics,³⁷ chemico-physical priors can accelerate generative compound design,⁷⁷ and causal priors can help to disentangle treatment effects from confounders.⁷⁹ These applications can expand the neuro-oncological therapeutic armamentarium and guide optimal patient allocation into prospective clinical trials based on patient characteristics beyond the standard inclusion criteria.³² Novel therapeutics demonstrating activity for selected CNS tumours require prospective evaluation alongside standard local therapies (eg, surgery, radiation therapy) to ensure their translation into meaningful improvements in clinical outcomes.

In the absence of data, generative models producing synthetic datasets might offer a resourceful alternative to extensive data collection; however, these models do not inherently ensure data realism. Extensive clinical validation can mitigate these concerns to some extent; nevertheless, the absence of mechanistic or causal models in synthetic data generation precludes unconditional generalisability. In contrast, models incorporating strict biophysical inductive biases might enable the parametrisation or simulation of

particular medical imaging modalities from first principles, thereby opening avenues for solving associated inverse problems such as recovering unknown parameters or states from observed measurements (eg, in histomolecular parameter estimation).²⁹ Furthermore, concurrent simulation of physiological and measurement processes (eg, neural activity and electroencephalography) might enable *in silico* experimentation with neural activity fingerprints in disease models,^{7,44} akin to strategies already used in *de novo* compound design and virtual screening.⁷⁷

Mitigating data gaps, and balancing innovation and AI regulation

Adopting and scaling up AI in neuro-oncology hinges on closing a tripartite data gap: collection (absence, scarcity, inaccessibility); standardisation (digitisation, storage, harmonisation); and annotation.

In most institutions, large, representative, and high-quality datasets are entirely absent, scarce (particularly for rare disease subtypes), or inaccessible to the wider research community owing to stringent data protection requirements. Collection and access of these datasets are crucial for model development and validation in multicentre international trials to ensure generalisability across institutions, regions, and patient groups. To counteract the overutilisation of small, biased samples—often in disfavour of minoritised and vulnerable groups—and to leverage existing and future AI applications in neuro-oncological care, broad data collection, representative patient population selection, and standardised dataset curation and processing are essential.^{42,80}

Existing data remain siloed due to inconsistent digitisation and the absence of standardised practices for recording, storage, centralisation, harmonisation, and deidentification. Variation between institutions, inconsistent data quality, and selection bias hinder the rapid validation and integration of novel algorithms into clinical settings owing to transfer penalties or performance deterioration upon deployment. Hence, neuro-oncological stakeholder groups promote the use of standardised data acquisition protocols and implementation of standard storage, digitisation, and processing practices.⁴²

Most AI applications to date are supervised—ie, the applications require annotated data for training. However, data labelling is often costly, arduous, and prone to inter-rater variability, particularly in neuropathology, in which data annotation is not a part of standard clinical routine. This annotation gap might be alleviated using AI-based auto-labelling pipelines—eg, leveraging pretrained foundation models adaptive to novel tasks with few annotated datapoints (panel 2).

AI-based decision support systems require prospective validation and seamless integration into routine neuro-oncological practice. The wealth of neuro-oncological AI research starkly contrasts with the conspicuous dearth of prospective validation studies and the paucity of AI applications receiving regulatory approval. Efforts are under way

to mitigate these validation and implementation gaps—eg, by hosting research community-wide tumour segmentation challenges as reported in a preprint paper,⁸¹ open-sourcing pretrained medical AI models,⁴⁷ and developing AI-based medical devices for several key neuro-oncological tasks (panel 3). Apart from validation studies, developers should align with existing regulatory frameworks (WHO,⁸² UNESCO,⁸³ and the Organisation for Economic Co-operation and Development)⁸⁴ to obtain regulatory approval and provide evidence suggesting that novel technologies indeed outperform existing workflows through meaningful improvements in clinical outcomes. Fast-track approval procedures by regulatory agencies (eg, the US Food and Drug Administration breakthrough device designation) offer opportunities for dynamic yet responsible innovation. Existing medical devices might serve as a roadmap to regulatory approval and financial viability for future applications (panel 3); reimbursement strategies need to balance patient outcomes and cost-effectiveness.⁸⁵ Devices without a clear pathway to regulatory approval (eg, generalist assistants) require the invention of flexible recertification pathways and novel governance frameworks. Guidelines should address fairness, reproducibility, robustness, and adherence to predefined ethical standards—anchored in human-centred, value-based, and equity-driven principles⁸⁶—while promoting balanced regulation that does not stifle innovation.

Conclusion

Integrating AI into neuro-oncological practice and research holds tremendous potential, as shown in areas such as non-invasive precision diagnosis and response assessment from clinical and non-routine imaging; translational inference; discovery of novel biomarkers and histomolecular tumour subclasses; treatment administration and monitoring; foundational research into druggable targets for incurable CNS neoplasms; risk stratification; and development of BCI-based neuro-rehabilitative devices. Exploratory future opportunities entail (generalist and agentic) neuro-oncology assistants, biophysical or causal modelling (eg, neural-cancer interactions), synthetic data generation, drug and drug target discovery, and patient stratification for the administration of tailored therapies. Development and deployment critically depend on addressing core challenges, including data gaps; clinical validation of assistive technologies and AI-based classification schemes; tissue-based corroboration of biomarkers; rooting generative models of data and disease in causal and biophysical insights; validation of druggable targets; and resolving core ethical, legal, and regulatory issues to ensure responsible, person-centred, equitable, and needs-based integration of AI-based tools into neuro-oncology.

Contributors

SV and SFW conceptualised and designed the study. SV designed and conducted the search strategy. SV, SFW, PK, EJV, MMK, TAN, PL, and NG drafted the manuscript. SV collated all contributions and revised the manuscript with support from SFW. All authors critically interpreted,

reviewed, edited, and commented on previous versions, approved the final version of this manuscript, and agreed to its publication. SV and SFW contributed equally to this work.

Declaration of interests

SV is an employee of QuantCo and may own stock as part of the standard compensation package. TAN receives consulting fees from Adya Health. EJV has received grants or contracts from Caris Life Sciences; consulting fees from Glasshouse Health and Servier Pharmaceuticals; is a member of the Data Safety Monitoring Board or Advisory Board of Servier Pharmaceuticals and NuvOx Pharma; is a member of ASTRO Finance and Audit Committee; and has received equipment, materials, drugs, medical writing, gifts, or other services from Caris Life Sciences. PL received speaker honoraria from Blue Earth Diagnostics; honoraria for Advisory Board participation from Servier Pharmaceuticals; and is a Chair of the EORTC Brain Tumor Group QA Committee. NG received speaker honoraria from Blue Earth Diagnostics; honoraria for Advisory Board participation at Telix Pharmaceuticals and Servier Pharmaceuticals; honoraria for consultancy services from Telix Pharmaceuticals; and is the Chair of the PET/RANO group and Chair of the EANO Publishing Activity Committee (both unpaid positions). SA and VN are employees of Alphabet and may own stock as part of the standard compensation package. MM holds equity in Maplight Therapeutics and CARGO Therapeutics. JD received royalties or licences from Wolters Kluwer (author for UpToDate); consulting fees from Novartis and Johnson & Johnson; and participated in a Data Safety Monitoring Board for Novartis and Janssen. All other authors declare no competing interests.

Data sharing

The code for the python APIs is available upon request to the corresponding author by any qualified investigator.

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References

- van den Bent MJ, Geurts M, French PJ, et al. Primary brain tumours in adults. *Lancet* 2023; **402**: 1564–79.
- Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep* 2012; **14**: 48–54.
- Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat Rev Clin Oncol* 2021; **18**: 170–86.
- Karschnia P, Smits M, Reifemberger G, et al. A framework for standardised tissue sampling and processing during resection of diffuse intracranial glioma: joint recommendations from four RANO groups. *Lancet Oncol* 2023; **24**: e438–50.
- Nelson TA, Dietrich J. Investigational treatment strategies in glioblastoma: progress made and barriers to success. *Expert Opin Investig Drugs* 2023; **32**: 921–30.
- van Solinge TS, Nieland L, Chiocca EA, Broekman MLD. Advances in local therapy for glioblastoma - taking the fight to the tumour. *Nat Rev Neurol* 2022; **18**: 221–36.
- Winkler F, Venkatesh HS, Amit M, et al. Cancer neuroscience: state of the field, emerging directions. *Cell* 2023; **186**: 1689–707.
- Hanahan D, Monje M. Cancer hallmarks intersect with neuroscience in the tumor microenvironment. *Cancer Cell* 2023; **41**: 573–80.
- Singhal K, Azizi S, Tu T, et al. Large language models encode clinical knowledge. *Nature* 2023; **620**: 172–80.
- Tu T, Azizi S, Driess D, et al. Towards generalist biomedical AI. *NEJM AI* 2024; **1**: A10a2300138.

- 11 Moses DA, Metzger SL, Liu JR, et al. Neuroprosthesis for decoding speech in a paralyzed person with anarthria. *N Engl J Med* 2021; **385**: 217–27.
- 12 Patel AP, Fisher JL, Nichols E, et al. Brain and other CNS cancer collaborators. Global, regional, and national burden of brain and other CNS cancer, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; **18**: 376–93.
- 13 Sosinsky A, Ambrose J, Cross W, et al. Insights for precision oncology from the integration of genomic and clinical data of 13,880 tumors from the 100,000 Genomes Cancer Programme. *Nat Med* 2024; **30**: 279–89.
- 14 Wang Z, Wang Y, Chang M, et al. Single-cell transcriptomic analyses provide insights into the cellular origins and drivers of brain metastasis from lung adenocarcinoma. *Neuro Oncol* 2023; **25**: 1262–74.
- 15 Gao P, Shan W, Guo Y, et al. Development and validation of a deep learning model for brain tumor diagnosis and classification using magnetic resonance imaging. *JAMA Netw Open* 2022; **5**: e2225608.
- 16 Li X, Strasser B, Neuberger U, et al. Deep learning super-resolution magnetic resonance spectroscopic imaging of brain metabolism and mutant isocitrate dehydrogenase glioma. *Neurooncol Adv* 2022; **4**: vda071.
- 17 van der Voort SR, Incekara F, Wijnenga MMJ, et al. Combined molecular subtyping, grading, and segmentation of glioma using multi-task deep learning. *Neuro Oncol* 2023; **25**: 279–89.
- 18 Vollmuth P, Foltyn M, Huang RY, et al. Artificial intelligence (AI)-based decision support improves reproducibility of tumor response assessment in neuro-oncology: an international multi-reader study. *Neuro Oncol* 2023; **25**: 533–43.
- 19 Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of tumors of the central nervous system: a summary. *Neuro Oncol* 2021; **23**: 1231–51.
- 20 Cluceru J, Interian Y, Phillips JJ, et al. Improving the noninvasive classification of glioma genetic subtype with deep learning and diffusion-weighted imaging. *Neuro Oncol* 2022; **24**: 639–52.
- 21 Zaragori T, Oster J, Roch V, et al. ¹⁸F-FDOPA PET for the noninvasive prediction of glioma molecular parameters: a radiomics study. *J Nucl Med* 2022; **63**: 147–57.
- 22 Tomaszewski MR, Gillies RJ. The biological meaning of radiomic features. *Radiology* 2021; **298**: 505–16.
- 23 Fan X, Li J, Huang B, et al. Noninvasive radiomics model reveals macrophage infiltration in glioma. *Cancer Lett* 2023; **573**: 216380.
- 24 Sun Q, Chen Y, Liang C, et al. Biologic pathways underlying prognostic radiomics phenotypes from paired MRI and RNA sequencing in glioblastoma. *Radiology* 2021; **301**: 654–63.
- 25 Yan J, Zhao Y, Chen Y, et al. Deep learning features from diffusion tensor imaging improve glioma stratification and identify risk groups with distinct molecular pathway activities. *EBiomedicine* 2021; **72**: 103583.
- 26 Xie X, Shen C, Zhang X, et al. Rapid intraoperative multi-molecular diagnosis of glioma with ultrasound radio frequency signals and deep learning. *EBiomedicine* 2023; **98**: 104899.
- 27 Cai S, Shi Z, Zhou S, et al. Cerebrovascular dysregulation in patients with glioma assessed with time-shifted BOLD fMRI. *Radiology* 2022; **304**: 155–63.
- 28 Calabrese E, Rudie JD, Rauschecker AM, Villanueva-Meyer JE, Cha S. Feasibility of simulated postcontrast MRI of glioblastomas and lower-grade gliomas by using three-dimensional fully convolutional neural networks. *Radiol Artif Intell* 2021; **3**: e200276.
- 29 Perlman O, Ito H, Herz K, et al. Quantitative imaging of apoptosis following oncolytic virotherapy by magnetic resonance fingerprinting aided by deep learning. *Nat Biomed Eng* 2022; **6**: 648–57.
- 30 Hollon T, Jiang C, Chowdury A, et al. Artificial-intelligence-based molecular classification of diffuse gliomas using rapid, label-free optical imaging. *Nat Med* 2023; **29**: 828–32.
- 31 Sanchez-Aguilera A, Masmudi-Martín M, Navas-Olive A, et al. Machine learning identifies experimental brain metastasis subtypes based on their influence on neural circuits. *Cancer Cell* 2023; **41**: 1637–49.e11.
- 32 Migliozi S, Oh YT, Hasanain M, et al. Integrative multi-omics networks identify PKC δ and DNA-PK as master kinases of glioblastoma subtypes and guide targeted cancer therapy. *Nat Cancer* 2023; **4**: 181–202.
- 33 Wang Z, Wang Y, Yang T, et al. Machine learning revealed stemness features and a novel stemness-based classification with appealing implications in discriminating the prognosis, immunotherapy and temozolomide responses of 906 glioblastoma patients. *Brief Bioinform* 2021; **22**: bbab032.
- 34 Wang W, Zhao Y, Teng L, et al. Neuropathologist-level integrated classification of adult-type diffuse gliomas using deep learning from whole-slide pathological images. *Nat Commun* 2023; **14**: 6359.
- 35 Zheng Y, Carrillo-Perez F, Pizurica M, Heiland DH, Gevaert O. Spatial cellular architecture predicts prognosis in glioblastoma. *Nat Commun* 2023; **14**: 4122.
- 36 Kondepudi A, Pekmezci M, Hou X, et al. Foundation models for fast, label-free detection of glioma infiltration. *Nature* 2025; **637**: 439–45.
- 37 Drexler R, Khatri R, Sauvigny T, et al. A prognostic neural epigenetic signature in high-grade glioma. *Nat Med* 2024; **30**: 1622–35.
- 38 Bahadir CD, Omar M, Rosenthal J, et al. Artificial intelligence applications in histopathology. *Nat Rev Electr Eng* 2024; **1**: 93–108.
- 39 Nasrallah MP, Zhao J, Tsai CC, et al. Machine learning for cryosection pathology predicts the 2021 WHO classification of glioma. *Med* 2023; **4**: 526–40.e4.
- 40 Vermeulen C, Pagès-Gallego M, Kester L, et al. Ultra-fast deep-learned CNS tumour classification during surgery. *Nature* 2023; **622**: 842–49.
- 41 Bakas S, Vollmuth P, Galldiks N, et al. Artificial Intelligence for Response Assessment in Neuro Oncology (AI-RANO), part 2: recommendations for standardisation, validation, and good clinical practice. *Lancet Oncol* 2024; **25**: e589–601.
- 42 Manjunath M, Yan J, Youn Y, et al. Functional analysis of low-grade glioma genetic variants predicts key target genes and transcription factors. *Neuro Oncol* 2021; **23**: 638–49.
- 43 Yang J, Wang Q, Zhang ZY, et al. DNA methylation-based epigenetic signatures predict somatic genomic alterations in gliomas. *Nat Commun* 2022; **13**: 4410.
- 44 Curry RN, Ma Q, McDonald MF, et al. Integrated electrophysiological and genomic profiles of single cells reveal spiking tumor cells in human glioma. *Cancer Cell* 2024; **42**: 1713–28.e6.
- 45 Krishna S, Choudhury A, Keough MB, et al. Glioblastoma remodelling of human neural circuits decreases survival. *Nature* 2023; **617**: 599–607.
- 46 Food and Drug Administration. Artificial intelligence and machine learning (AI/ML)-enabled medical devices. 2025. <https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices> (accessed Jan 26, 2025).
- 47 Kiraly AP, Baur S, Philbrick K, et al. Health AI developer foundations. *arXiv* 2024; published online Nov 22. <https://arxiv.org/abs/2411.15128> (preprint).
- 48 Huynh E, Hosny A, Guthrie C, et al. Artificial intelligence in radiation oncology. *Nat Rev Clin Oncol* 2020; **17**: 771–81.
- 49 Savjani RR, Lauria M, Bose S, et al. Automated tumor segmentation in radiotherapy. *Semin Radiat Oncol* 2022; **32**: 319–29.
- 50 Connor M, Kim MM, Cao Y, Hattangadi-Gluth J. Precision radiotherapy for gliomas: implementing novel imaging biomarkers to improve outcomes with patient-specific therapy. *Cancer J* 2021; **27**: 353–63.
- 51 Karschnia P, Young JS, Dono A, et al. Prognostic validation of a new classification system for extent of resection in glioblastoma: a report of the RANO resect group. *Neuro Oncol* 2023; **25**: 940–54.
- 52 Khan DZ, Luengo I, Barbarisi S, et al. Automated operative workflow analysis of endoscopic pituitary surgery using machine learning: development and preclinical evaluation (IDEAL stage 0). *J Neurosurg* 2021; **137**: 1–8.
- 53 Pandya S, Motkoski JW, Serrano-Almeida C, et al. Advancing neurosurgery with image-guided robotics. *J Neurosurg* 2009; **111**: 1141–49.
- 54 Naik A, Smith AD, Shaffer A, et al. Evaluating robotic pedicle screw placement against conventional modalities: a systematic review and network meta-analysis. *Neurosurg Focus* 2022; **52**: E10.
- 55 Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with BRAF^{V600E}-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. *Lancet Oncol* 2022; **23**: 53–64.

- 56 Lam KHB, Leon AJ, Hui W, et al. Topographic mapping of the glioblastoma proteome reveals a triple-axis model of intra-tumoral heterogeneity. *Nat Commun* 2022; **13**: 116.
- 57 Wang Y, Luo R, Zhang X, et al. Proteogenomics of diffuse gliomas reveal molecular subtypes associated with specific therapeutic targets and immune-evasion mechanisms. *Nat Commun* 2023; **14**: 505.
- 58 Isaev K, Jiang L, Wu S, et al. Pan-cancer analysis of non-coding transcripts reveals the prognostic onco-lncRNA HOXA10-AS in gliomas. *Cell Rep* 2021; **37**: 109873.
- 59 Liu XP, Jin X, Seyed Ahmadian S, et al. Clinical significance and molecular annotation of cellular morphometric subtypes in lower-grade gliomas discovered by machine learning. *Neuro Oncol* 2023; **25**: 68–81.
- 60 Cimino PJ, Ketchum C, Turakulov R, et al. Expanded analysis of high-grade astrocytoma with piloid features identifies an epigenetically and clinically distinct subtype associated with neurofibromatosis type 1. *Acta Neuropathol* 2023; **145**: 71–82.
- 61 Métais A, Bouchoucha Y, Kergrohen T, et al. Pediatric spinal pilocytic astrocytomas form a distinct epigenetic subclass from pilocytic astrocytomas of other locations and diffuse leptomeningeal glioneuronal tumours. *Acta Neuropathol* 2023; **145**: 83–95.
- 62 Auffret L, Ajlil Y, Tauziède-Espariat A, et al. A new subtype of diffuse midline glioma, H3 K27 and BRAF/FGFR1 co-altered: a clinico-radiological and histomolecular characterisation. *Acta Neuropathol* 2023; **147**: 2.
- 63 Vaios EJ, Winter SF, Shih HA, et al. Novel mechanisms and future opportunities for the management of radiation necrosis in patients treated for brain metastases in the era of immunotherapy. *Cancers (Basel)* 2023; **15**: 2432.
- 64 Gonzalez Castro LN, Liu I, Filbin M. Characterizing the biology of primary brain tumors and their microenvironment via single-cell profiling methods. *Neuro Oncol* 2023; **25**: 234–47.
- 65 Moassefi M, Faghani S, Conte GM, et al. A deep learning model for discriminating true progression from pseudoprogression in glioblastoma patients. *J Neurooncol* 2022; **159**: 447–55.
- 66 Zhao J, Vaios E, Wang Y, et al. Dose-incorporated deep ensemble learning for improving brain metastasis stereotactic radiosurgery outcome prediction. *Int J Radiat Oncol Biol Phys* 2024; **120**: 603–13.
- 67 Kim MM, Aryal MP, Sun Y, et al. Response assessment during chemoradiation using a hypercellular/hyperperfused imaging phenotype predicts survival in patients with newly diagnosed glioblastoma. *Neuro Oncol* 2021; **23**: 1537–46.
- 68 Ellingson BM, Hagiwara A, Morris CJ, et al. Depth of radiographic response and time to tumor regrowth predicts overall survival following anti-VEGF therapy in recurrent glioblastoma. *Clin Cancer Res* 2023; **29**: 4186–95.
- 69 Zhang H, Zhang N, Wu W, et al. Machine learning-based tumor-infiltrating immune cell-associated lncRNAs for predicting prognosis and immunotherapy response in patients with glioblastoma. *Brief Bioinform* 2022; **23**: bbac386.
- 70 Meißner AK, Gutsche R, Galldiks N, et al. Radiomics for the non-invasive prediction of PD-L1 expression in patients with brain metastases secondary to non-small cell lung cancer. *J Neurooncol* 2023; **163**: 597–605.
- 71 Winter SF, Vaios EJ, Shih HA, et al. Mitigating radiotoxicity in the central nervous system: role of proton therapy. *Curr Treat Options Oncol* 2023; **24**: 1524–49.
- 72 Reyes-González J, Barajas-Olmos F, García-Ortiz H, et al. Brain radiotoxicity-related 15CacBRT gene expression signature predicts survival prognosis of glioblastoma patients. *Neuro Oncol* 2023; **25**: 303–14.
- 73 Willett FR, Avansino DT, Hochberg LR, Henderson JM, Shenoy KV. High-performance brain-to-text communication via handwriting. *Nature* 2021; **593**: 249–54.
- 74 Tang J, LeBel A, Jain S, Huth AG. Semantic reconstruction of continuous language from non-invasive brain recordings. *Nat Neurosci* 2023; **26**: 858–66.
- 75 Ammari S, Bône A, Balleyguier C, et al. Can deep learning replace gadolinium in neuro-oncology? A reader study. *Invest Radiol* 2022; **57**: 99–107.
- 76 Gagnon L, Gupta D, Mastorakos G, et al. Deep learning segmentation of infiltrative and enhancing cellular tumor at pre- and posttreatment multishell diffusion MRI of glioblastoma. *Radiol Artif Intell* 2024; **6**: e230489.
- 77 Wang H, Fu T, Du Y, et al. Scientific discovery in the age of artificial intelligence. *Nature* 2023; **620**: 47–60.
- 78 WHO. Ethics and governance of artificial intelligence for health: guidance on large multi-modal models. Jan 18, 2024. <https://iris.who.int/bitstream/handle/10665/375579/9789240084759-eng.pdf> (accessed Jan 26, 2025).
- 79 Bica I, Alaa AM, Lambert C, van der Schaar M. From real-world patient data to individualized treatment effects using machine learning: current and future methods to address underlying challenges. *Clin Pharmacol Ther* 2021; **109**: 87–100.
- 80 Kim MM, Mehta MP, Smart DK, et al. National Cancer Institute Collaborative Workshop on Shaping the Landscape of Brain Metastases Research: challenges and recommended priorities. *Lancet Oncol* 2023; **24**: e344–54.
- 81 LaBella D, Schumacher K, Mix M, et al. Brain tumor segmentation (brats) challenge 2024: meningioma radiotherapy planning automated segmentation. *arXiv* 2024; published online August 15. <https://arxiv.org/abs/2405.18383> (preprint).
- 82 WHO. Regulatory considerations on artificial intelligence for health. Oct 19, 2023. <https://iris.who.int/bitstream/handle/10665/373421/9789240078871-eng.pdf> (accessed Jan 26, 2025).
- 83 UNESCO. Recommendation on the ethics of artificial intelligence. Sept 26, 2024. <https://unesdoc.unesco.org/ark:/48223/pf0000380455> (accessed Jan 26, 2025).
- 84 The Organisation for Economic Co-operation and Development. Collective action for responsible AI in health. Jan 19, 2024. https://www.oecd.org/content/dam/oecd/en/publications/reports/2024/01/collective-action-for-responsible-ai-in-health_9a65136f/f2050177-en.pdf (accessed Jan 26, 2025).
- 85 Parikh RB, Helmchen LA. Paying for artificial intelligence in medicine. *NPJ Digit Med* 2022; **5**: 63.
- 86 Mehari M, Sibih Y, Dada A, et al. Enhancing neuro-oncology care through equity-driven applications of artificial intelligence. *Neuro-Oncology* 2024; **26**: 1951–63.

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