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REVIEW ARTICLE

# Artificial Intelligence in Neuro-Oncology: predicting molecular markers and response to therapy.

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## ABSTRACT

Artificial intelligence's capability to analyze and interpret complex data is transforming neuro-oncology by enhancing the precision of diagnosis and enabling personalized treatment plans. Particularly, applications in radiogenomics are instrumental in identifying molecular markers from imaging data, potentially reducing the need for invasive procedures and accelerating molecular diagnostics. This review discusses various artificial intelligence methodologies, from machine learning to deep learning, mentioning a number of their current use cases and the challenges faced in clinical integration. In addition, future directions, such as multimodal data integration and the need to address technical and ethical implications, are highlighted.

**Keywords:** Radiogenomic, Neuro-oncology, Artificial Intelligence, Treatment.

## Introduction

The emergence of artificial intelligence (AI) in healthcare, particularly in neuro-oncology, marks a transformative shift in traditional medical practices. AI technologies are increasingly integrated into various aspects of patient care, from diagnostics to treatment planning[1–3]. In neuro-oncology, AI's ability to analyze complex medical data rapidly and precisely offers significant promise. It can identify subtle patterns in imaging, genetic information, and clinical data that might elude human detection, leading to better diagnosis of tumors. Furthermore, AI-driven models can predict patients' responses to various treatments, enabling personalized therapy regimens that are tailored to individual genetic profiles and disease characteristics[4–6].

Imaging techniques are rapidly advancing as non-invasive technologies, becoming increasingly essential in the diagnosis and prognosis of various diseases. The use of radiological imaging data to predict genomic and molecular markers, known as radiogenomics, facilitates accurate lesion categorization and treatment planning. Additionally, the application of AI techniques to imaging for predicting genomic information or treatment responses—often imperceptible to the human eye—is emerging as a prominent research area in the intersection of AI and medicine. Also, compared to conventional tumor imaging sequences (including T1-weighted imaging (T1WI), T2WI, T2 fluid-attenuated inversion recovery (FLAIR), and contrast-enhanced T1WI), advanced MRI techniques, such as diffusion, perfusion, and spectroscopy, can provide additional information about the tumor's pathophysiology, which enhances diagnostic and prognostic insights and aids in targeted histopathological evaluation[7,8]. Introducing these new techniques, which reflect additional information, has created new opportunities for applying AI.

This paper provides a comprehensive review of AI imaging technologies in neuro-oncology. We aim to illustrate if AI has the potential to enhance the precision and effectiveness of treatments by leveraging predictive analytics to assess molecular markers and predict therapeutic outcomes. This review highlights the crucial role of radiological imaging as a tool in the AI-enhanced diagnostic and treatment processes within neuro-oncology.

## Foundations of AI in Medicine:

A broad range of technologies designed to mimic human cognition in analyzing, interpreting, and comprehending complex data is encompassed by AI. Machine learning (ML), as a part of AI, is characterized by machine algorithms that can autonomously identify intricate patterns in data, execute tasks, and incrementally enhance their pattern recognition using gathered information. Deep learning (DL), a subset of ML, consists of multiple layers of interconnected artificial neurons that autonomously learn to represent features from data. This occurs without the necessity for manual feature engineering, which sets it apart from traditional ML algorithms[9,10].

In medical applications, AI technologies are employed for different tasks, including segmentation, object detection, classification, and generation. Segmentation is the process of semantically dividing individual pixels of an

image into areas of interest and background, which is crucial in medical imaging for isolating organs or quantifying abnormalities such as tumors. By applying this technique, tumor volumetric measurements can be accurately performed. Object detection identifies and locates objects within an image using rectangular bounding boxes but does not precisely delineate the tumor. Classification categorizes what is present in the image, such as 'glioblastoma(GBM)' or 'lymphoma', 'normal white matter', etc. Generative AI creates new images or data from existing datasets, which is valuable for expanding datasets to train AI systems.(Figure-1)

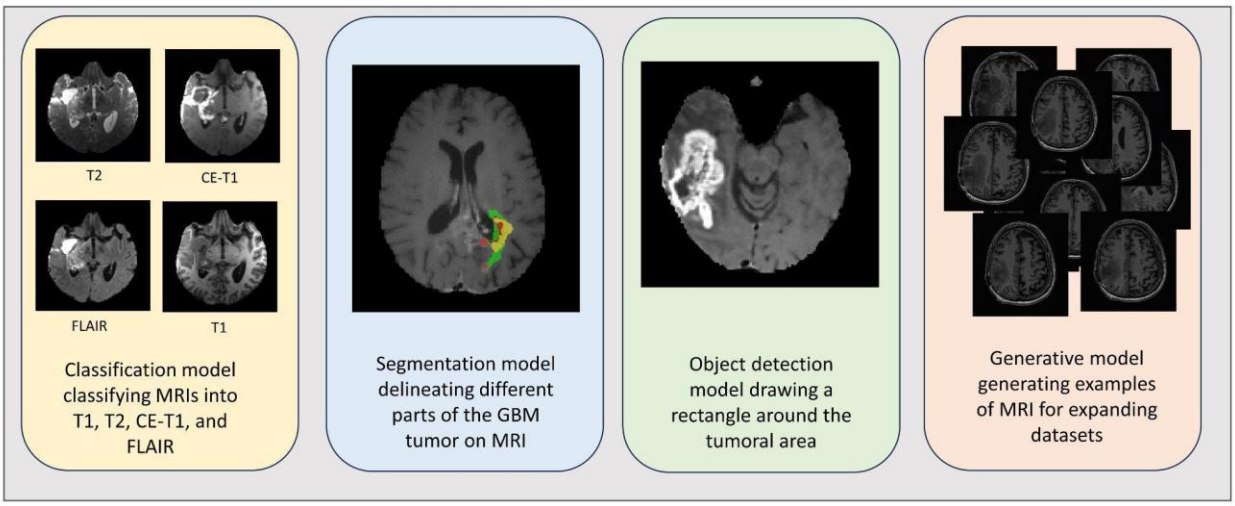


*Figure 1 - Examples of Different AI Model Types: T1-weighted (T1), T2-weighted (T2), Fluid-Attenuated Inversion Recovery (FLAIR), Contrast-Enhanced T1-weighted (CE-T1), Glioblastoma (GBM), Magnetic Resonance Imaging (MRI).*

Another way to categorize AI models in medicine involves classifying them based on their medical tasks. Diagnostic models, for example, may be designed to predict genomic or epigenomic information directly from imaging data, a task beyond human capability. Prognostic models utilize imaging alone or in combination with non-image data (models that use different kinds of data are called multimodal models), including molecular and clinical information, to assess disease prognosis or evaluate patient survival. Lastly, there are models that assess treatment response, which determines whether a treatment is affecting a tumor and possibly estimates the magnitude of the response. These may be intermingled in various applications, such as a model that diagnoses a tumor grade and predicts a genomic biomarker. These can then be used to provide a prognosis, all of which may influence treatment planning[11].

It is important to note that to develop an accurate AI model, a sufficiently large dataset of images paired with labels like genomic or molecular information for each case is essential. The dataset must be high-quality and diverse enough to enable the model to learn different patterns for accurate prediction and ideally be sourced from multiple institutions with diverse populations. Multi-institutional datasets ensure models' generalizability and applicability across different institutions.

## Radiogenomics

Genetic mutations play a crucial role in the development of brain tumors; changes in

cellular genes might transform normal cells into cancerous ones. In modern medicine, with detailed tumor classification and various treatment options, identifying these mutations during diagnosis is crucial for selecting the optimal treatment[12]. The traditional and gold-standard methods for assessing molecular markers typically involve obtaining tissue samples and conducting histological assays to determine genomic or epigenomic profiles. However, brain tumor resection may not always be safe based on the tumor location, and biopsy-based methods can lead to complications. Consequently, noninvasive alternatives are crucial for acquiring genetic and histologic information. Radiogenomics operates on the underlying assumption that subtle, often undetectable patterns in medical imaging may correlate with genomic and epigenomic markers. AI models aim to capture this subtle quantitative information and transform it into valid genomic predictions.

The most-studied molecular marker in brain tumors is isocitrate dehydrogenase (IDH) mutation status. The IDH 1 and 2 enzymes oxidize isocitrate to α-ketoglutarate and thus play a crucial role in energy production and maintaining the redox balance of the cell. Mutations in the genes for these enzymes (IDH1 and IDH2) are strongly linked to glioma and other forms of cancer and are associated with distinct clinical characteristics. Patients presenting with gliomas carrying the IDH-wildtype gene typically face a poorer prognosis than those with IDH mutations[13]. The most common methods for detecting IDH mutations are immunohistochemistry and Sanger DNA sequencing, though a wide range of other DNA-based techniques also exist[14,15]. While Sanger sequencing has a low limit of detection, next-generation sequencing remains prohibitively expensive. Therefore, the search continues for a reliable and robust pathological gold standard[16,17]. Numerous studies have been published that utilize ML algorithms and imaging to detect or classify glioma tumors into IDH mutated or wild type, reporting varying levels of success[18]. A meta-analysis of 26 studies involving 3,280 patients found that radiomics features had a pooled sensitivity of 79% (95% CI: 76, 83) and specificity of 80% (95% CI: 76, 83) for detecting IDH mutations[19]. Another study using three centers' datasets applied ML techniques and achieved an 85.45% accuracy rate in classifying IDH status[20]. One study showed that training models to classify IDH and 1p19q-codeletion status (evaluating multiple molecular markers) could detect the genomic mutation better than a single gene, with an overall accuracy of 85.7%. They also used diffusion-weighted MRI and showed that using those sequences rather than anatomical images improved accuracy to 88.8%[21].(Figure-2)

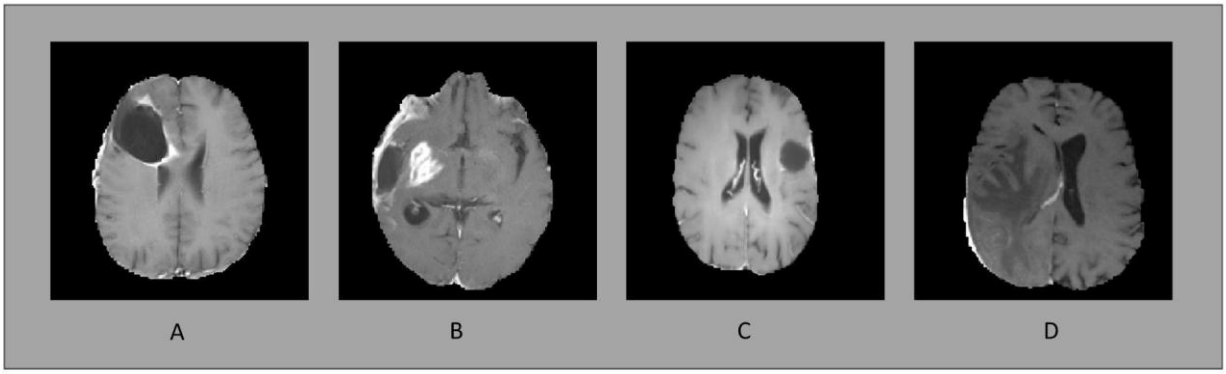


*Figure 2 - Images A and B display tumors characterized by wild-type isocitrate dehydrogenase (IDH), while images C and D show examples of IDH mutated. Artificial Intelligence is employed to identify and distinguish patterns in these tumors that may not be readily apparent to the human eye.*

Radiogenomics has also been applied to pediatric neurooncology. For instance, diagnosing medulloblastoma (MB) subgroups through molecular marker categorization provides a noninvasive, presurgical approach to MB risk stratification[22]. The status of these molecular subgroups predicts prognosis and unlocks the potential for more precise treatment. In MB patients, the Wingless (WNT) pathway, when mutated, generally leads to better outcomes and may allow for less aggressive treatment approaches. The Sonic Hedgehog (SHH) pathway varies more in its implications based on age and specific mutation subtype, influencing treatment and prognosis differently. The other two categories, group 3 and group 4 tumors, are often provisionally bundled as non-WNT and non-SHH MB due to a lack of identification of driver mutations[23]. A retrospective study involving MRI data from pediatric patients across 12 international sites used ML to differentiate these clinically relevant MB subgroups—WNT, SHH, Group 3, and Group 4—with impressive precision. By extracting 1800 radiomic features from T2 and contrast-enhanced T1-weighted scans, the study developed a two-stage classifier that effectively distinguished non-WNT and non-SHH subgroups and then further identified WNT from SHH with a binary F1 score of 95% for WNT, demonstrating its superior diagnostic ability. Another classifier differentiated high-risk Group 3 from Group 4 with an AUC of 98%, showcasing the potential of AI to provide noninvasive, presurgical insights that could influence treatment plans and potentially lead to more targeted genetic analyses, all while avoiding the complications and limitations associated with invasive and expensive molecular testing[24].

Other genomic factors, including 1p/19q co-deletion, Tumor Protein 53, and B-Raf proto-oncogene, among others, are critical in diagnosing and prognosticating neuro-oncological diseases[25–28]. We have highlighted only a select few studies in the field of radiogenomics detection; a comprehensive review of all examples is beyond our scope.

## AI in Predicting Response to Therapy

The ability of AI to predict the effectiveness of treatment early in the process can result in optimizing treatment regimens and could

spare patients from ineffective therapies. For instance, AI algorithms can analyze historical treatment data alongside real-time patient data to predict how a patient might respond to a particular therapy based on genetic, phenotypic, and clinical characteristics[29–31]. This predictive capability enables oncologists to tailor treatments more precisely and to make informed decisions about whether to continue, adjust, or halt a given therapeutic strategy. This approach enhances the potential for successful outcomes and plays a role in personalized medicine, where treatment plans are increasingly based on individual patient profiles rather than standard protocols.

An important AI application in neuro-oncology is its use in predicting treatment response by differentiating pseudoprogression (PsP) from true progression (TP) in patients with GBM. PsP and TP often manifest similar imaging characteristics; however, PsP typically stabilizes or resolves without the need for aggressive treatment, whereas TP demands more intensive management. This distinction is vital, as it directly impacts treatment decisions and patient outcomes[32]. Currently, there is no gold standard imaging technique or feature that can reliably distinguish between PSP and TP. One recent example demonstrating the capabilities of DL, a 3D-Densenet121 model distinguished PsP from TP that were considered indeterminate by neuroradiologists with a 76.4% accuracy, highlighting the potential of AI to interpret complex multi-parametric MRI data effectively[6]. Liu et al. introduced an ensemble DL model that utilized weighted gradients to enhance MRI analysis, achieving 90.20% accuracy. They also visualized maps of MRI regions to boost interpretability and gain clinician trust[33]. Adding to the arsenal, Li et al. deployed a deep convolutional generative adversarial network that distinguished the imaging features of PsP versus TP with a notable accuracy of 92%[34]. AI's utility extends to other imaging methods, such as amino acid positron emission tomography imaging and ML algorithms that analyze dynamic contrast-enhanced and diffusion-weighted imaging, offering deeper insights into GBM post-treatment behavior[35,36]. The ongoing refinement and validation of these AI models are crucial to ensure their successful integration into clinical practice.

Predicting treatment response in brain metastasis is another use case for AI algorithms. Notably, they are used in managing patients with brain metastases undergoing stereotactic radiosurgery (SRS). Utilizing ML models that integrate multimodal MRI radiomics and clinical risk factors, researchers have demonstrated exceptional capability in identifying patients at risk of local failure post-SRS, achieving predictive accuracies with AUC values as high as 0.95[37]. This showcases how ML models analyze patient-specific, multi-modal information to avoid treatment options likely to fail. Furthermore, AI-driven tools such as MEtastasis Tracking with Repeated Observations (METRO), which automatically measures the largest 3D tumor diameter, enhance the tracking and measurement of brain metastases, correlating highly with traditional manual methods and offering more reliable assessments of treatment efficacy[38]. Technologies such as these represent a significant leap forward in customizing and enhancing care for patients with brain metastases.

## Practical Considerations

The application of published models in radiology faces significant barriers, including the availability of high-quality ground truth data, the creation of generalizable, reproducible, and interpretable methods that are robust to the continued improvements/changes in MRI techniques, and the incorporation of these methods into practical workflows. Addressing each of these challenges requires tailored, case-specific solutions[39]. Here, we outline several of these considerations and barriers.

One of the primary struggles in AI research is the need for robust and homogenously annotated datasets, as studies with small sample sizes can lead to measurement bias. In medical AI, data acquisition is costly, and the dependency on large, well-labeled datasets makes training supervised models challenging. Currently, most neuro-oncology imaging research areas other than gliomas face challenges due to a lack of publicly available datasets, with much of the data compartmentalized within various organizations and hospital systems. To improve the generalizability of algorithm performance across different imaging sites, acquisition parameters, and patient demographics, more extensive and diverse datasets are needed. Although collaborative efforts like the Cancer Imaging Archive(TCIA) platform help to address these issues by pooling resources to create models, data and model sharing remain complicated by concerns over patient safety[40].

Another challenge is the inability to replicate reported results due to the unavailability of detailed methods, program code, and access to datasets[41–43]. Different results obtained using alternative datasets further complicate matters. To address these issues, authors should be encouraged to provide their code and, ideally, their datasets along with their manuscripts or at least include detailed descriptions as per published checklists to ensure adequate transparency[44–46]. Applying these models in clinical settings remains highly problematic or even unfeasible without the ability to reproduce and validate results.

The potential for bias in AI-related studies is also a challenge. To gain a comprehensive understanding of the clinical efficacy of these models, systematic reviews and meta-analyses with precise bias assessments are essential to differentiate between studies with low and high bias. A few manuscripts have been released claiming to achieve nearly 100% accuracy in detecting previously described IDH mutation using MRI. Despite employing sophisticated AI techniques, these papers may suffer from various flaws, such as data leakage, small sample sizes, and randomly achieved acceptable results. While achieving an accuracy rate above 90% may appear promising, it should be approached cautiously as it may not consistently deliver dependable results[39,40,47]. To highlight the importance of bias assessment, another recent systematic review exploring the literature concerning predicting MGMT status using AI assessed the risk of bias in these studies. They found that despite the apparent functionality of models in this area, 27% of the published studies were classified as high-risk for bias. This classification was based on factors such as dataset size, preprocessing methodologies, modeling techniques, and reporting intricacies[48]. External validation and thorough bias detection reviews are two imperative steps required for clinical utilization.

The rapid evolution of medical imaging acquisition techniques poses a significant challenge to the widespread adoption and longitudinal use of AI models in radiology. In one study comparing GBM segmentation performance on 3D fast spin echo versus inversion recovery gradient echo MRI sequences, AI models trained on specific imaging protocols exhibited substantially degraded performance when applied to data from different acquisitions[49]. Another publication by Ellingson et al. highlighted the critical need for standardized brain tumor imaging protocols in clinical trials to ensure consistent image quality and interpretation across sites[50]. However, integrating such protocols with additional clinically desired sequences while accounting for variability in scanner hardware and software versions remains an ongoing obstacle for reliable AI deployment over time and at different centers with diverse imaging equipment. Overcoming this obstacle is crucial for realizing the full potential of AI in radiological practice. When institutions consider implementing an AI model, it's crucial for them to conduct a comprehensive evaluation to determine if the model performs effectively within their unique operational context. This involves testing the model's compatibility with existing systems and verifying its accuracy and reliability in their specific environment. Such assessments help ensure that the AI application enhances their workflows and meets their clinical or operational requirements. (Table-1)

| Challenges | Ways to Overcome |
|---|---|
| Lack of robust and homogeneously annotated datasets | Collaborative efforts like the TCIA platform to pool resources and create larger, diverse datasets. |
| Inability to replicate reported results due to lack of code, detailed methods, and access to datasets | Encourage authors to provide code, datasets, and detailed descriptions following published checklists. |
| Potential for bias in AI-related studies | Systematic reviews and meta-analyses with precise bias assessments to differentiate between low and high-bias studies. |
| Rapid evolution of medical imaging acquisition techniques | Standardized imaging protocols in clinical trials, accounting for scanner hardware and software variability. |
| Ensuring AI model compatibility and performance in specific operational contexts | Comprehensive evaluation of model compatibility with existing systems, accuracy, and reliability in the specific environment. |

***Table 1:*** *Challenges and Ways to Overcome in the Use of AI in Neuro-Oncology (with The Cancer Imaging Archive (TCIA))*

## Future Directions and Conclusion

Future research should focus on addressing the challenges associated with the deployment of AI models in clinical settings. This includes enhancing the quality and diversity of training datasets to improve the robustness and generalizability of AI systems across different populations and imaging technologies. Collaborative efforts between medical institutions and AI researchers are crucial to amass large-scale, annotated datasets that reflect the wide spectrum of clinical scenarios encountered in practice.

Moreover, developing standardized protocols for AI applications in neuro-oncology will ensure consistent and reliable results. These protocols should include guidelines for data collection, model training, and validation processes that adhere to rigorous scientific and ethical standards. As AI models become more integrated into clinical workflows, continuous monitoring, and evaluation will be necessary to assess their impact on patient outcomes and to refine their predictive capabilities.

In conclusion, AI holds the promise of revolutionizing the field of neuro-oncology by enhancing the accuracy of molecular diagnostics and the efficacy of treatment protocols. By continuing to leverage AI in conjunction with radiogenomics and advanced imaging techniques, healthcare professionals can better understand the complex biological behaviors of brain tumors and tailor treatments to individual patient needs. The journey towards fully realizing the potential of AI in neuro-oncology will require persistent innovation, interdisciplinary collaboration, and commitment to improving patient care.

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None.

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## Abbreviations:

- Artificial Intelligence (AI)
- Fluid-Attenuated Inversion Recovery (FLAIR)
- T1-Weighted Imaging (T1WI)
- Machine Learning (ML)
- Deep Learning (DL)
- Glioblastoma (GBM)
- Isocitrate Dehydrogenase (IDH)
- Medulloblastoma (MB)
- Wingless (WNT)
- Sonic Hedgehog (SHH)
- Pseudoprogression (PsP)
- True Progression (TP)
- O6-methylguanine-DNA methyltransferase (MGMT)
- The Cancer Imaging Archive(TCIA)

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