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Artificial Intelligence Enabled Imaging Biomarkers for Distinguishing Pseudoprogression from True Progression after Cellular Immunotherapy in Glioblastoma

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Systematic Review

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Abstract

Pseudoprogression, transient radiographic worsening caused by treatment-related inflammation rather than tumor growth, is a well-recognized pitfall after chemoradiotherapy for glioblastoma and is becoming more relevant as checkpoint inhibitors and cellular immunotherapies such as chimeric antigen receptor (CAR) T cells enter clinical testing. Conventional structural magnetic resonance imaging (MRI) cannot reliably separate pseudoprogression from true progression, exposing patients to premature treatment discontinuation or unnecessary intensification. Quantitative, artificial-intelligence-based imaging analysis (radiomics, and its molecular extension radiogenomics) is an emerging candidate solution. In this narrative review we synthesize the evidence on radiomics and radiogenomics for differentiating pseudoprogression from true progression in glioblastoma, with emphasis on the immunotherapy and cellular-therapy context. We summarize the pathobiology and reported frequency of pseudoprogression after standard and immune-based therapies, outline the limitations of current response criteria (RANO, iRANO, RANO 2.0), and review representative studies of texture analysis, hand-crafted radiomics, deep-learning radiomics, and radiogenomics. Although several studies report promising discrimination (reported area-under-the-curve values of approximately 0.88-0.92 in different cohorts), the evidence is limited by small sample sizes, retrospective designs, inconsistent definitions and protocols, and infrequent external validation. Progress will require prospective multicenter cohorts with standardized acquisition and segmentation, adherence to TRIPOD and CLAIM reporting standards, transparent and interpretable models, and integration with clinical, molecular, and liquid-biopsy data. A dedicated evidence base specific to cellular immunotherapy is urgently needed.

Key Points

MRI cannot reliably separate pseudoprogression from true progression.

Radiomics shows promise but lacks external validation in glioblastoma.

Cellular immunotherapy needs standardized imaging studies.

1. Introduction

Glioblastoma (GBM) is the most common and most lethal primary malignant brain tumor in adults. The current standard of care, maximal safe resection followed by radiotherapy with concomitant and adjuvant temozolomide, has remained the backbone of treatment since the pivotal trial of Stupp and colleagues, yet virtually all tumors recur [1]. The 2021 World Health Organization classification integrates histology with molecular markers, notably IDH status, but therapeutic options for the IDH-wildtype tumors that dominate the adult GBM population remain limited [2].

Response assessment has evolved in parallel. The Response Assessment in Neuro-Oncology (RANO) criteria introduced standardized, MRI-based definitions of progression [3]. Recognition that immunotherapy can produce delayed responses and atypical radiographic patterns prompted the immunotherapy RANO (iRANO) criteria, which require confirmatory imaging after apparent early progression [4]. RANO 2.0 subsequently simplified and modernized the criteria for high- and low-grade gliomas [5].

Immunotherapy has created a new interpretive challenge. Checkpoint inhibitors have modest single-agent activity in GBM, but immunogenomic analyses have clarified determinants of response and motivated combinatorial and neoadjuvant strategies [6]. Cellular immunotherapy has advanced further: first-in-human studies of CAR T cells targeting IL13Ralpha2 and, more recently, EGFRvIII/EGFR (CARv3-TEAM-E) showed rapid radiographic responses, albeit often transient, and established intracavitary and intraventricular delivery as feasible [7,8]. Imaging will therefore increasingly need to interpret treatment effects in patients receiving therapies whose mechanisms differ fundamentally from chemotherapy.

Pseudoprogression (PsP) is defined as an increase in enhancement or edema that mimics progressive disease but resolves or stabilizes without a change in therapy, reflecting treatment-related inflammation and blood-brain-barrier disruption rather than tumor growth [9]. After standard chemoradiotherapy, PsP is most frequent in the first months after radiation and is associated with MGMT promoter methylation and IDH-mutant status [10,11]. In the immunotherapy era its frequency is debated: a meta-analysis of checkpoint-inhibitor trials across solid tumors estimated a pooled pseudoprogression incidence of approximately 6% [12], and a dedicated analysis of 55 ICI-treated GBM patients found no convincing evidence of pseudoprogression with ICI monotherapy [13], although durable disease control after initial radiographic worsening has been reported in individual patients [14]. For cellular immunotherapy, whose local inflammatory effects are intense, the radiographic patterns and optimal time windows for declaring progression are even less well characterized [8,15]. Misclassification has direct consequences: labeling true progression as pseudoprogression delays salvage therapy, whereas labeling pseudoprogression as progression can terminate an effective treatment prematurely [9,15].

In this narrative review we examine whether and how AI-enabled imaging biomarkers (radiomics and radiogenomics) can help distinguish PsP from true progression (TP) in GBM, with particular attention to the cellular-immunotherapy context. We summarize the assessment framework and its limitations, review the radiomics and radiogenomics evidence, and propose a roadmap toward clinically useful, externally validated decision support.

2. Pseudoprogression in the era of immunotherapy and cellular therapy

2.1 Pathobiology and frequency after standard therapy

PsP after radiotherapy and temozolomide is generally attributed to subacute radiation injury: endothelial damage, blood-brain-barrier disruption, vasogenic edema, and inflammatory-cell infiltration produce transient contrast enhancement on MRI [9] (Fig. 1). Reported frequencies vary widely across series because of differences in definition, imaging timing, and use of biopsy confirmation; retrospective analyses of conventionally treated GBM cohorts have identified early post-treatment imaging changes meeting PsP criteria in a substantial minority of patients [10,11]. Molecular features modulate this risk: MGMT promoter methylation and IDH mutation are associated with a higher likelihood of PsP and with a better prognosis, complicating the interpretation of radiographic endpoints in clinical trials [10,11].

2.2 Checkpoint inhibition

The pattern, and even the existence, of PsP during checkpoint-inhibitor therapy for GBM remains debated. In extracranial solid tumors, a systematic review and meta-analysis of prospective ICI studies found a pooled pseudoprogression incidence of approximately 6% (95% CI 5–7%) [12]. In GBM specifically, retrospective data suggest that ICI monotherapy rarely produces true PsP: in a series of 55 patients treated with ICI for recurrent or newly diagnosed disease, no convincing PsP attributable to ICI monotherapy was identified, prompting caution against prolonged continuation of ineffective therapy based on an assumed pseudoprogression [13]. Nevertheless, individual patients have achieved long-term disease control after an initial radiographic worsening during nivolumab treatment, indicating that immune-related inflammatory change can occur in the central nervous system and that confirmatory imaging remains essential before abandoning therapy [14]. These observations underpin the iRANO recommendation that apparent progression within the first six months of immunotherapy should be confirmed by follow-up imaging before treatment is discontinued [4].

2.3 Cellular immunotherapy

Cellular therapies, particularly CAR T cells, generate a qualitatively different on-target inflammatory response. Infusion-site inflammation, cytokine release, and immune-cell infiltration can produce rapid and dramatic MRI changes that are difficult to classify with conventional criteria [8,15]. In the first reported patient with multifocal recurrent GBM treated with IL13Ralpha2-directed CAR T cells, all intracranial and spinal tumors regressed after intracavitary and intraventricular infusions [7]. In the INCIPIENT study of intraventricular CARv3-TEAM-E T cells, three patients with recurrent GBM showed rapid radiographic regression within days of a single infusion, but responses were transient in two of the three [8]. These small studies highlight two imaging problems: distinguishing early true progression from treatment-related inflammation, and distinguishing durable response from transient inflammatory improvement followed by regrowth. Because cellular-therapy trials in GBM remain small and early, no validated imaging criteria exist for this setting, and current practice borrows from frameworks designed for chemotherapy and checkpoint inhibition [5,8,15].

3. Response assessment and its imaging limitations

Conventional structural MRI (T1-weighted contrast-enhanced and T2/FLAIR sequences) remains the backbone of response assessment. RANO and RANO 2.0 define measurable disease, generally require at least a 25% increase in enhancing tumor for progression, and incorporate clinical status and corticosteroid use [3,5]. These criteria were designed primarily for the chemotherapy era and have recognized limitations: they treat new enhancement as potentially progressive regardless of cause, they are vulnerable to measurement variability, and they do not capture the biological heterogeneity of the underlying tissue [5]. iRANO added an immunotherapy-specific overlay but retained structural MRI as the primary readout [4].

Advanced MRI can partially overcome these limitations by probing physiology rather than morphology. Perfusion-weighted MRI estimates cerebral blood volume and permeability, which are generally higher in active tumor than in treatment effect; a meta-analysis of perfusion MRI for differentiating glioma recurrence from PsP reported pooled sensitivity of 0.88 and specificity of 0.77 across 11 studies and 416 patients [16]. Diffusion-weighted and diffusion-kurtosis imaging reflect cellularity and microstructural complexity, and combining diffusion-kurtosis parameters with dynamic susceptibility contrast perfusion improved discrimination in a small single-center study (reported area under the curve [AUC] 0.924 for the combined model) [17]. Texture analysis of conventional sequences has also shown promise; for example, a study of 22 patients reported that gray-level co-occurrence

matrix features on T2-weighted imaging distinguished TP from PsP with AUC values of approximately 0.88–0.89 [18]. Amino-acid PET with FET provides complementary metabolic information: a radiomics model applied to dynamic FET PET in 34 patients after chemoradiation was reported to identify all PsP cases in the test cohort, although the cohort was small and augmented [19].

These physiological and metabolic markers are informative, but they are operator- and protocol-dependent, are often evaluated in small single-center cohorts, and have not been integrated into a widely adopted clinical workflow. They are, however, a natural substrate for quantitative, reproducible feature extraction, which is the premise of radiomics.

4. Radiomics for pseudoprogression versus true progression

Radiomics converts medical images into large numbers of quantitative features (intensity, shape, texture, and higher-order statistics) that can be mined with machine-learning models. Applied to the PsP-versus-TP problem in glioma, the workflow typically comprises tumor segmentation, feature extraction, feature selection, classifier training, and, ideally, validation on independent data.

Several studies illustrate both the promise and the limitations of this approach. In a retrospective study of 77 GBM patients (51 TP, 26 PsP) treated with standard chemoradiotherapy, a random-forest classifier built from 9,675 texture features extracted from T1-weighted contrast-enhanced MRI distinguished TP from PsP with a reported accuracy of approximately 73% [20]. A more recent multicenter study integrated hand-crafted radiomics with features from a pretrained convolutional network (ConvNeXt Tiny) into a deep-learning radiomics nomogram; in 293 glioma patients (208 TP, 85 PsP), the combined model achieved an AUC of 0.908 in the test set and outperformed both the individual signatures and the assessments of senior radiologists [21]. Multiparametric MRI-based scoring systems have likewise been proposed for high-grade glioma [22].

Across these and related studies (Table 1), reported performance is generally good (AUC values of roughly 0.85–0.92 in the test cohorts described above), yet several caveats recur: small and heterogeneous cohorts; retrospective designs with referral and verification bias; inconsistent definitions of PsP (radiographic versus biopsy-confirmed); variable timing of imaging relative to treatment; and, most importantly, infrequent external validation [20,21,22]. A recent narrative review specifically addressing AI-driven radiomics and radiogenomics for PsP after cellular immunotherapy in GBM reached similar conclusions: although radiomics features from multiple MRI sequences correlate with cell density, vascularity, immune-cell concentration, and molecular status, clinical translation is constrained by inconsistent protocols, small cohorts, insufficient external validation, limited model interpretability, and inconsistent reference standards [23]. That review also emphasized that combining imaging features with liquid biopsy, genomic data, and electronic health records could improve diagnostic accuracy and yield surrogate markers for immune-checkpoint and CAR-T trials [23].

Table 1
Representative studies of imaging biomarkers for distinguishing pseudoprogression from true progression in glioma

Study (year)	Population and setting	Imaging / features	Method	Reported performance	Key limitations
Chen et al. (2015) [18]	22 GBM after RT + TMZ	GLCM texture of conventional MRI (T1, T2, FLAIR, T1-CE)	Texture-feature thresholds	T2 contrast/correlation features: AUC 0.883/0.892; accuracy 86.4%	Small cohort; single center; no external validation
Wan et al. (2017) [16]	Meta-analysis: 11 studies, 416 patients	Perfusion MRI (DSC/DCE)	Pooled diagnostic meta-analysis	Pooled sensitivity 0.88; specificity 0.77; SROC AUC 0.89	Heterogeneous protocols
Lohmann et al. (2020) [19]	34 patients (94% IDH-wt) after chemoradiation	Dynamic FET PET radiomics (944 features; 102 datasets after augmentation)	Radiomics model (up to 4 features)	100% sensitivity / 100% NPV for PsP in the test cohort	Very small cohort; data augmentation; no external validation
Sun et al. (2021) [20]	77 GBM after standard treatment (51 TP, 26 PsP)	T1-CE radiomics (9,675 texture features)	Random forest	Accuracy approximately 72.8%	Single center; modest accuracy; no external validation
Shi et al. (2021) [17]	34 high-grade gliomas within 6 months after treatment	DKI + DSC MRI	Multivariate logistic regression	Combined rMK + rCBV: AUC 0.924; accuracy 88.2%	Small single-center cohort
Zheng et al. (2026) [21]	Multicenter; 293 gliomas (208 TP, 85 PsP)	Multiparametric MRI; hand-crafted radiomics + ConvNeXt Tiny deep features	Deep-learning radiomics nomogram	Test AUC 0.908; outperformed radiologists	Retrospective; further external validation needed
Ghorbani et al. (2026) 22	Prospective; 30 high-grade glioma patients after standard treatment	Multiparametric MRI: DSC, IVIM, MRS, and anatomical imaging	Multiparametric scoring system (MSS)	AUC 0.958; sensitivity 87.5%; specificity 92.9%	Small prospective cohort; external validation needed

TP, true progression; PsP, pseudoprogression; RT, radiotherapy; TMZ, temozolomide; GLCM, gray-level co-occurrence matrix; DKI, diffusion kurtosis imaging; DSC, dynamic susceptibility contrast; SROC, summary receiver operating characteristic; AUC, area under the curve; NPV, negative predictive value; CE, contrast-enhanced; IDH-wt, IDH-wildtype. Performance metrics are as reported in the cited publications and have not been re-derived by the authors.

These limitations are characteristic of the radiomics field more broadly, in which methodological quality, rather than algorithmic sophistication, is the principal determinant of clinical usefulness [24]. Small single-center studies with internally cross-validated models tend to overstate generalizability, and features are sensitive to acquisition parameters, field strength, and segmentation method [24]. Reporting is heterogeneous, and adherence to established reporting standards is uncommon.

5. Radiogenomics: imaging phenotypes as molecular and immune surrogates

Radiogenomics aims to link imaging phenotypes to molecular characteristics, using MRI as a noninvasive window onto tumor biology. In GBM, machine-learning analysis of multiparametric, multiregional MRI features has been shown to classify molecular characteristics such as DNA-methylation subgroups, MGMT promoter methylation, and hallmark copy-number alterations with moderate-to-good accuracy in single-institution cohorts [25]. Because PsP risk is molecularly modulated, most clearly by MGMT promoter methylation and IDH status, imaging features that reflect these molecular states could help estimate the a priori likelihood that new enhancement represents treatment effect rather than progression [10,11,25].

The immune microenvironment is a second, highly relevant axis. GBM is infiltrated by tumor-associated macrophages and microglia that shape tumor behavior and response to therapy [6]. Radiogenomics analyses have begun to connect quantitative MRI parameters with immune-cell gene expression: in a study of 60 GBM patients, expression of myeloid markers such as CD68 and CSF1R correlated positively with normalized cerebral blood volume, and CD49d expression was independently associated with progression-free survival [26]. Such imaging-immune associations suggest that MRI phenotypes could identify an immune-active tumor in which new enhancement after cellular therapy is more likely to reflect inflammatory response than resistant regrowth [23,26]. These hypotheses remain exploratory and require prospective validation before they can inform treatment decisions.

6. Toward multimodal decision support after cellular immunotherapy

No single modality is likely to resolve the PsP-versus-TP question after cellular immunotherapy, given the complexity of the underlying biology. A realistic path forward is multimodal integration: (i) serial structural and advanced MRI with standardized acquisition; (ii) quantitative radiomics and radiogenomics features; (iii) molecular information (MGMT, IDH, and emerging immune signatures); and (iv) liquid-biopsy biomarkers such as circulating tumor DNA in plasma or cerebrospinal fluid, which can track tumor burden and emerging resistance in ways that structural imaging alone cannot [23] (Fig. 2). Temporal modeling is equally important: because PsP is by definition transient, longitudinal trajectories of imaging and molecular features may provide more robust discrimination than single time-point snapshots [23].

For cellular immunotherapy specifically, several design considerations follow from the early CAR T-cell data. First, baseline imaging before infusion should be standardized and, where feasible, combined with baseline molecular and liquid-biopsy sampling [8,23]. Second, early post-infusion scans should be interpreted with the expectation of inflammatory change, and suspected progression should trigger protocol-defined confirmatory imaging rather than immediate treatment discontinuation [4,8]. Third, response definitions must accommodate transient improvement followed by regrowth, a pattern observed with CARv3-TEAM-E cells [8]. Finally, imaging and molecular datasets from cellular-therapy trials, including the small number of patients treated to date, should be pooled prospectively to build the evidence base needed for population-specific biomarkers [15,23].

7. Challenges and a roadmap to clinical translation

The principal barriers to clinical use of radiomics-based PsP biomarkers are methodological rather than technological. Radiomics features are sensitive to acquisition parameters and segmentation, and models developed in small single-center cohorts rarely generalize [24]. Internal cross-validation is frequently mistaken for external validation, and reporting is heterogeneous. We propose the following roadmap.

1. **Standardized acquisition and segmentation.** Multicenter protocols with harmonized MRI parameters and robust, ideally automated, segmentation, with explicit reporting of scanner and sequence details [23,24].
2. **Transparent model development and reporting.** Adherence to the TRIPOD statement for prediction models and the CLAIM checklist for artificial intelligence in medical imaging, including prespecified definitions of PsP and TP, handling of verification bias, and reporting of calibration as well as discrimination [27,28].
3. **External and prospective validation.** Independent, geographically distinct test sets followed by prospective collection, because retrospective single-center estimates consistently overstate real-world performance [21,24,28].
4. **Interpretability and clinical integration.** Models should provide per-patient explanations and decision-curve analyses demonstrating net benefit over current practice, such as the treating radiologist or an iRANO-based algorithm [21,27].
5. **Immunotherapy- and cellular-therapy-specific cohorts.** Dedicated registries and trial-embedded imaging substudies with paired liquid biopsy, because PsP biology and frequency after cellular therapy cannot be inferred from chemoradiotherapy-era data [8,13,15,23].
6. **Methodological quality assessment.** Routine use of available quality tools to audit published radiomics studies and guide reviewers [24].

Without these steps, promising AUC values will continue to fail the transition from retrospective research to clinical decision support.

8. Conclusions

Pseudoprogression after treatment of glioblastoma is a clinically consequential diagnostic problem that is becoming more complex as checkpoint inhibitors and, in particular, cellular immunotherapies enter practice. Radiomics and radiogenomics offer a principled approach to extracting quantitative, biologically informative signatures from MRI that could help distinguish treatment-related change from true progression. Published studies report encouraging discrimination, but the field is constrained by small, retrospective, heterogeneous cohorts and limited external validation. The most urgent need is a prospective, multicenter, multimodal evidence base specific to cellular immunotherapy, built on standardized imaging, transparent reporting (TRIPOD/CLAIM), external validation, interpretable models, and integration with molecular and liquid-biopsy data. Until such evidence exists, AI-enabled imaging biomarkers for pseudoprogression should be regarded as promising decision-support tools rather than established clinical tests.

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Ethics Approval: Not applicable; this review did not involve human participants or animals.

Patient Consent Statement (Informed Consent): Not applicable; this review did not involve human participants or identifiable patient data.

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Clinical Trial Registration: Not applicable; this is a narrative review and does not report a clinical trial.

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Figures

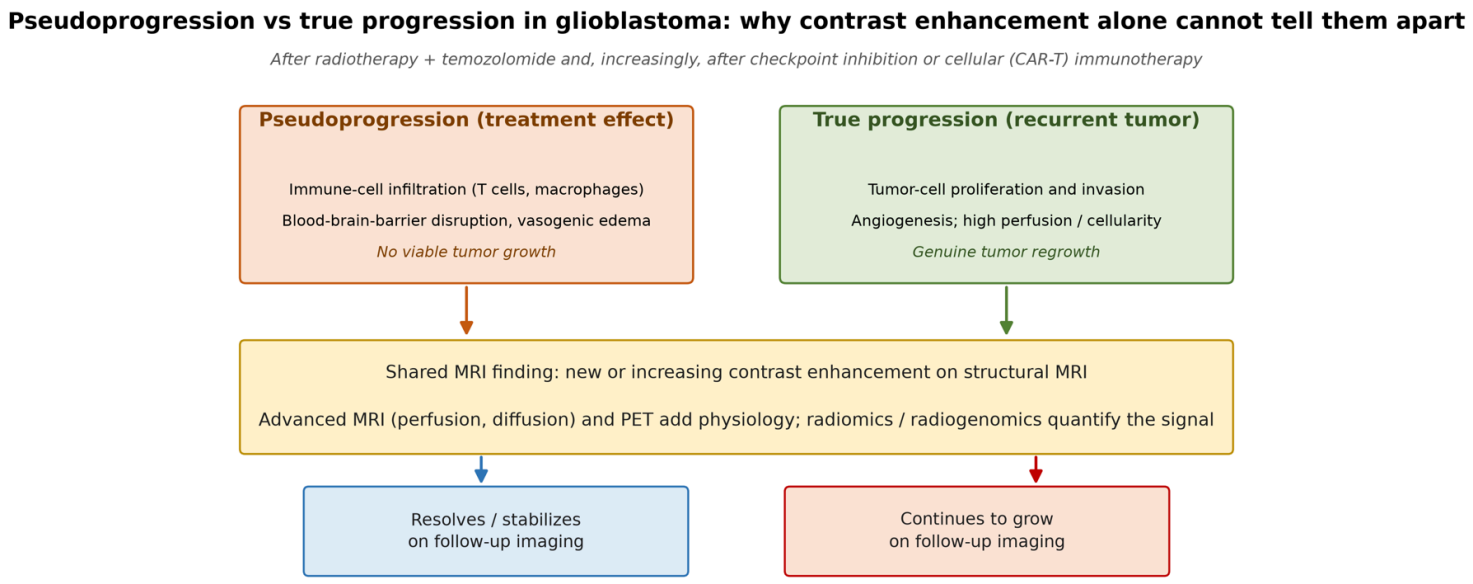


Figure 1

Pseudoprogression versus true progression in glioblastoma: mechanisms and imaging signatures. Schematic representation of the cellular and vascular events underlying treatment-related pseudoprogression (inflammation, blood-brain-barrier disruption, edema) and true progression (tumor-cell proliferation, angiogenesis) after standard chemoradiotherapy and after cellular immunotherapy (CAR T-cell infiltration and cytokine-mediated inflammation), and the imaging features that quantitative analysis aims to disentangle.

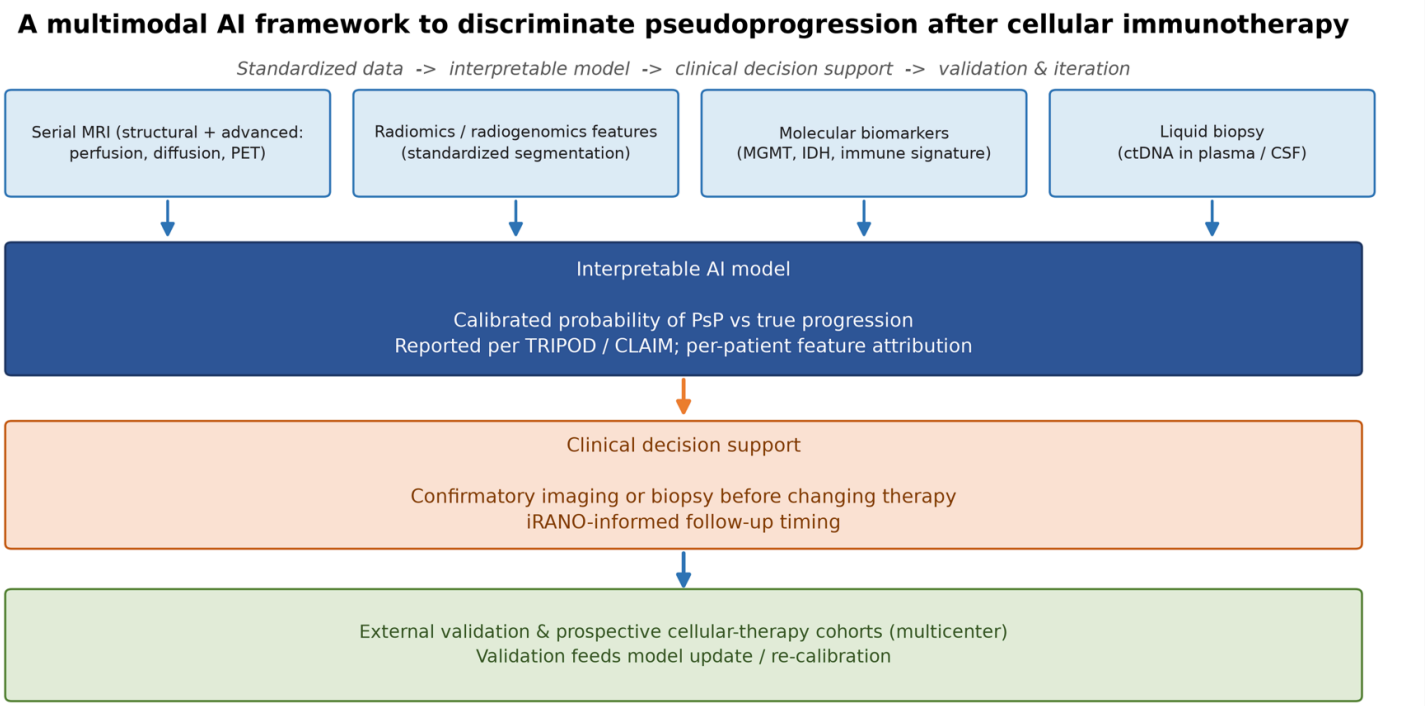


Figure 2

Proposed multimodal framework for AI-enabled discrimination of pseudoprogression after cellular immunotherapy. Conceptual diagram integrating serial structural and advanced MRI, radiomics and radiogenomics features, molecular biomarkers, and liquid biopsy (circulating tumor DNA) into an interpretable decision-support model with external validation and prospective trial deployment.

Supplementary Files

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- table3immunecorr.csv
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- fig2lassopath.png
- fig3lassocv.png
- fig4kmtrain.png
- fig5kmvalidation.png
- fig6auc.png
- fig7multivariateforest.png
- fig8riskdistribution.png
- fig9immunecorr.png