



NEURORADIOLOGY OF ADULT-TYPE DIFFUSE GLIOMAS IN THE MOLECULAR ERA: A NARRATIVE REVIEW OF IMAGING BIOMARKERS, RESPONSE ASSESSMENT AND ARTIFICIAL INTELLIGENCE

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Neurorradiologia de gliomas difusos do tipo adulto na era molecular: uma revisão narrativa
sobre biomarcadores de imagem, avaliação de resposta e inteligência artificial

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ABSTRACT

Background. The fifth edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System, published in 2021, reorganised adult diffuse gliomas around molecular rather than purely histological criteria. Neuroradiology has consequently shifted from a descriptive discipline concerned with grade and mass effect to one expected to contribute genotype-relevant information, quantify residual and recurrent disease, and adjudicate ambiguous post-treatment findings. **Objective.** To synthesise, in narrative form, the current role of neuroradiology in adult-type diffuse gliomas, covering acquisition standardisation, structural and advanced imaging biomarkers, radiogenomics, response assessment criteria and artificial intelligence (AI). **Methods.** We searched PubMed for English-language articles indexed up to September 2026, combining terms for diffuse glioma, the WHO 2021 classification, individual imaging techniques, response assessment and machine learning. Priority was given to consensus statements of the Response Assessment in Neuro-Oncology (RANO) group and allied societies, diagnostic test-accuracy meta-analyses, multicentre validation studies and randomised trials with imaging endpoints. Selection was purposive rather than systematic, as befits a narrative review. **Findings.** Standardised acquisition remains the rate-limiting step for every quantitative biomarker. Among structural signs, the T2-FLAIR mismatch sign is near-specific but insensitive for astrocytoma, IDH-mutant (pooled sensitivity 42%, specificity 100% across 12 studies and 1,053 patients). Advanced techniques are complementary rather than interchangeable: relative cerebral blood volume distinguishes grades imperfectly when assessed against a rigorous reference standard, 2-hydroxyglutarate spectroscopy detects IDH mutation with wide confidence intervals, amide proton transfer-weighted imaging performs competitively for IDH status and grading, and amino acid positron emission tomography (PET) outperforms MRI for post-treatment recurrence and identifies measurable disease in far more patients than contrast enhancement does. RANO 2.0 unified response assessment across grades, and PET RANO 1.0 provides the first structured framework for amino acid PET. AI has reached credible multicentre performance for segmentation, volumetric response and molecular prediction, but external validation, protocol heterogeneity and reporting quality remain limiting. **Conclusion.** No single imaging biomarker substitutes for molecular pathology. The realistic contribution of neuroradiology is a standardised, multiparametric and increasingly automated workflow that stratifies patients, quantifies disease burden and resolves post-treatment ambiguity.

Keywords: Glioma; Magnetic resonance imaging; neuroradiology; neuro-oncology; isocitrate dehydrogenase; radiomics; positron-emission tomography; response assessment in neuro-oncology.

RESUMO

Contexto. A quinta edição da Classificação de Tumores do Sistema Nervoso Central da Organização Mundial da Saúde (OMS), publicada em 2021, reorganizou os gliomas difusos em adultos com base em critérios moleculares, em vez de puramente histológicos. Consequentemente, a neurorradiologia passou de uma disciplina descritiva, preocupada com o grau e o efeito de massa, para uma que deve contribuir com informações relevantes sobre o genótipo, quantificar a doença residual e recorrente e arbitrar achados ambíguos pós-tratamento. **Objetivo.** Sintetizar, em formato narrativo, o papel atual da neurorradiologia em gliomas difusos do tipo adulto, abrangendo padronização da aquisição de imagens, biomarcadores de imagem estruturais e avançados, radiogenômica, critérios de avaliação de resposta e inteligência artificial (IA). **Métodos.** Pesquisamos no PubMed artigos em inglês indexados até setembro de 2026, combinando termos para glioma difuso, classificação da OMS de 2021, técnicas de imagem individuais, avaliação de resposta e aprendizado de máquina. Foi dada prioridade às declarações de consenso do grupo de Avaliação de Resposta em Neuro-Oncologia (RANO) e sociedades afins, metanálises de precisão de testes diagnósticos, estudos de validação multicêntricos e ensaios randomizados com desfechos de imagem. A seleção foi intencional em vez de sistemática, como convém a uma revisão narrativa. **Resultados.** A aquisição padronizada continua sendo a etapa limitante para todos os biomarcadores quantitativos. Entre os sinais estruturais, o sinal de discrepância T2-FLAIR é quase específico, mas pouco sensível para astrocitoma com mutação IDH (sensibilidade agrupada de 42%, especificidade de 100% em 12 estudos e 1.053 pacientes). As técnicas avançadas são complementares, e não intercambiáveis: o volume sanguíneo cerebral relativo distingue os graus de forma imperfeita quando avaliado em relação a um padrão de referência rigoroso; a espectroscopia de 2-hidroxiglutarato detecta a mutação IDH com amplos intervalos de confiança; a imagem ponderada por transferência de prótons amida tem desempenho competitivo para o status e classificação do IDH; e a tomografia por emissão de pósitrons (PET) de aminoácidos supera a ressonância magnética (RM) para recorrência pós-tratamento e identifica doença mensurável em muito mais pacientes do que o contraste. O RANO 2.0 unificou a avaliação da resposta em todos os graus, e o PET RANO 1.0 fornece a primeira estrutura estruturada para PET de aminoácidos. A IA atingiu um desempenho multicêntrico confiável para segmentação, resposta volumétrica e previsão molecular, mas a validação externa, a heterogeneidade do protocolo e a qualidade dos relatórios ainda são limitações. **Conclusão:** Nenhum biomarcador de imagem isolado substitui a patologia molecular. A contribuição realista da neurorradiologia é um fluxo de trabalho padronizado, multiparamétrico e cada vez mais automatizado que estratifica pacientes, quantifica a carga da doença e resolve ambiguidades pós-tratamento.

Palavras-chave: Glioma; ressonância magnética; neurorradiologia; neuro-oncologia; isocitrato desidrogenase; radiômica; tomografia por emissão de pósitrons; avaliação da resposta em neuro-oncologia.

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INTRODUCTION

Diffuse gliomas are the most frequent malignant primary tumours of the central nervous system in adults, and their management has changed more in the past decade than in the preceding half-century. The decisive event was the publication in 2021 of the fifth edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System, which subordinated histology to molecular alteration in the definition of tumour types and, for the first time, allowed a molecular finding alone to determine grade^[1]. Adult-type diffuse gliomas were reduced from a heterogeneous family of astrocytomas, oligodendrogliomas and mixed lesions to three entities: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype^[1]. European and international clinical guidelines were revised accordingly^[2,6].

For neuroradiology, this reorganisation is not a nomenclature problem but an epistemological one. A report that concludes “low-grade glioma” no longer names a diagnosis, because the same T2-hyperintense, non-enhancing lesion may correspond to a tumour with a median survival measured in decades or in a few years depending

on IDH and 1p/19q status^[3,4,5]. At the same time, the questions asked of imaging have multiplied. Clinicians now expect the radiologist to suggest a molecular class before surgery, to quantify the extent of resection in a way that can be pooled across trials, to distinguish treatment effect from progression in a patient receiving radiotherapy, temozolomide, an antiangiogenic agent, an immunotherapy or a mutant IDH inhibitor, and to do so with measurements reproducible enough to serve as trial endpoints.

This narrative review examines how far neuroradiology has travelled towards those expectations. We first address acquisition standardisation, which conditions everything downstream. We then review structural signs with molecular value, the principal advanced techniques and their evidence base, the radiogenomics of individual markers, the surgical and post-treatment settings, the evolution of response assessment criteria culminating in RANO 2.0 and PET RANO 1.0, and finally the state of artificial intelligence (AI) in this field. Table 1 summarises the advanced imaging techniques, their biological substrate, clinical application and limitations; Table 2 assembles representative studies retrieved from PubMed with their principal quantitative results.

Table 1. Advanced imaging techniques in adult-type diffuse gliomas: biological substrate, principal metrics, clinical application and limitations.

Technique	Biological substrate	Principal metric(s)	Main clinical application in diffuse glioma	Principal limitations	Ref.
Conventional structural MRI (BTIP)	Tissue T1/T2 relaxation; blood-brain barrier integrity	Bidimensional and volumetric enhancing and non-enhancing tumour; T2-FLAIR mismatch sign	Detection, localisation, surgical planning, baseline and follow-up measurement for RANO	Enhancement is a non-specific surrogate of tumour activity; grade cannot be inferred reliably; protocol adherence variable	7, 9, 10, 45
Diffusion-weighted imaging (DWI)	Water mobility, inversely related to cellular density	Apparent diffusion coefficient (ADC), minimum and mean values	Cellularity estimation; contribution to IDH prediction; discrimination of progression from pseudoprogression	Wide inter-group overlap; sensitive to necrosis, haemorrhage and oedema; threshold not transferable	21, 41
Diffusion tensor imaging (DTI)	Directional water diffusion along white-matter tracts	Fractional anisotropy, mean diffusivity; tractography	Presurgical mapping of eloquent tracts; early detection of structural change under chemotherapy	Algorithm-dependent reconstruction; degraded by oedema and prior surgery; crossing-fibre ambiguity	23, 37
Diffusion kurtosis imaging (DKI)	Non-Gaussian diffusion reflecting microstructural complexity	Mean kurtosis, kurtosis fractional anisotropy	Grading (grade 4 vs 2-3); adjunct to IDH prediction	Does not separate grade 2 from grade 3; longer acquisition; outperformed by APTw in direct comparison	24
Dynamic susceptibility contrast (DSC) perfusion	Microvascular density and blood volume; contrast leakage	Relative cerebral blood volume (rCBV); percentage signal recovery (PSR)	Grading; IDH prediction (PSR); target selection for biopsy; post-treatment discrimination	rCBV threshold of 1.75 unreliable against rigorous reference standard; requires preload and leakage correction; protocol-dependent	19, 20, 21, 41
Dynamic contrast-enhanced (DCE) perfusion	Blood-brain barrier permeability	Ktrans, ve, vp	Permeability assessment; complementary grading information	Pharmacokinetic model dependence; sparse comparative evidence; not represented in quantitative synthesis	19

Technique	Biological substrate	Principal metric(s)	Main clinical application in diffuse glioma	Principal limitations	Ref.
Arterial spin labelling (ASL)	Cerebral blood flow, without exogenous contrast	Tumour blood flow, normalised to normal-appearing tissue	Contrast-free grading and surveillance; recognition of treatment complications including radiation necrosis	Low signal-to-noise ratio; transit-time sensitivity; less standardised than DSC	22
MR spectroscopy (2-HG)	Accumulation of the oncometabolite D-2-hydroxyglutarate in IDH-mutant tumours	2-HG resonance at ~2.25 ppm; Cho/NAA ratios	Direct non-invasive detection of IDH mutation; potential pharmacodynamic marker for mutant IDH inhibitors	Small cohorts and wide confidence intervals; demands large voxels, high field and expert spectral fitting; limited availability	25, 26
Amide proton transfer-weighted (APT _w) CEST	Mobile amide protons of cytosolic proteins and peptides; tissue pH	CEST ratio (CESTR), normalised CESTR, relaxation-compensated MTR	IDH prediction and grading; discrimination of recurrence from pseudoprogression; intralesional heterogeneity mapping	Poor at separating oligodendroglioma from astrocytoma; vendor-specific thresholds; limited multicentre data	24, 27, 28
Amino acid PET (18F-FET, 11C-MET, 18F-FDOPA)	Upregulated L-type amino acid transport, largely independent of barrier disruption	Tumour-to-background ratio (TBR); time-activity curve dynamics; PET-positive volume	Differentiation of recurrence from treatment-related change; definition of measurable disease and biopsy targeting; prognostication	Tracer availability, cost and on-site production; radiation exposure; thresholds vary by tracer and protocol	29, 30, 31, 32, 33, 34
Synthetic / quantitative MRI	Intrinsic T1 and T2 relaxation times and proton density	T1 and T2 relaxation times, proton density percentiles	Objective, operator-independent alternative to visual signs such as T2-FLAIR mismatch	Single small cohort evidence in this indication; sequence and vendor dependence	18
Functional MRI (task-based and resting-state)	Neurovascular coupling in eloquent cortex	BOLD activation maps; functional connectivity	Presurgical mapping to preserve function while maximising resection	Neurovascular uncoupling in vascular tumours; task compliance; not a replacement for intraoperative mapping	37
Radiomics and deep learning on MRI	Quantitative texture, shape and intensity patterns; learned representations	AUC for molecular class; Dice coefficient; automated volumes	Automated segmentation and volumetric response; molecular stratification; synthetic contrast and accelerated acquisition	Retrospective single-vendor training; scarce external validation; feature instability; poor reporting quality	49, 50, 51, 52, 54, 55

APT_w, amide proton transfer-weighted; ASL, arterial spin labelling; AUC, area under the receiver operating characteristic curve; BOLD, blood-oxygen-level dependent; BTIP, standardised Brain Tumor Imaging Protocol; CEST, chemical exchange saturation transfer; Cho, choline; DCE, dynamic contrast-enhanced; DKI, diffusion kurtosis imaging; DSC, dynamic susceptibility contrast; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; IDH, isocitrate dehydrogenase; MTR, magnetisation transfer ratio; NAA, N-acetylaspartate; PET, positron emission tomography; PSR, percentage signal recovery; RANO, Response Assessment in Neuro-Oncology; rCBV, relative cerebral blood volume; TBR, tumour-to-background ratio; 2-HG, 2-hydroxyglutarate.

Table 2. Representative studies retrieved from PubMed, with design, sample and principal quantitative findings.

Study (first author, year)	Journal	Design	Sample	Technique / index	Principal quantitative finding	Ref.
Patel, 2017	Clin Cancer Res	Retrospective, two independent readers; separate validation cohort	125 (TCGA/TCIA) + 82 (institutional) lower-grade gliomas	T2-FLAIR mismatch sign	All 15 positive cases were IDH-mutant, 1p/19q non-codeleted: PPV 100%, NPV 54%; validation cohort PPV 100%, NPV 76%	10
Broen, 2018	Neuro Oncol	Multicentre validation study, 3 databases	154 genotyped lower-grade gliomas	T2-FLAIR mismatch sign	Interrater kappa 0.75; sensitivity 51%, specificity 100%, PPV 100%, NPV 68%	11
Park, 2021	Eur Radiol	Systematic review and diagnostic meta-analysis	12 studies, 1,053 patients	T2-FLAIR mismatch sign	Pooled sensitivity 42% (95% CI 28-58), specificity 100% (95% CI 88-100); HSROC AUC 0.77	12
Kikuchi, 2024	Neuroradiology	Retrospective comparison of readers, 3D CNN and relaxometry	33 IDH-mutant gliomas (19 astrocytoma, 14 oligodendroglioma); CNN trained on 50 additional cases	T2-FLAIR mismatch sign; synthetic MRI relaxometry	Readers sensitivity/specificity 76.3%/100% (AUC 0.880) vs CNN 94.7%/92.9% (AUC 0.938); combined T1/T2 threshold 94.4%/100% (AUC 0.981)	18
Abrigo, 2018	Cochrane Database Syst Rev	Cochrane diagnostic test-accuracy review with individual-participant data	7 studies, 115 participants (83 low-grade, 32 high-grade)	DSC perfusion rCBV, threshold 1.75	Summary sensitivity 0.83 (95% CI 0.66-0.93), specificity 0.48 (95% CI 0.09-0.90); evidence judged insufficient for reliable estimation	19
Cindil, 2022	Acad Radiol	Retrospective, 3 T multiparametric MRI	58 histologically proven high-grade gliomas	ADC, rCBV, percentage signal recovery (PSR)	PSR best single predictor of IDH status: AUC 0.938, accuracy 0.87; PSR + rCBV combined AUC 0.955; ADC significant but overlapping	21
Choi, 2012	Nat Med	Prospective technique development with tissue correlation	30 patients with glioma	Optimised proton MRS for 2-HG	Non-invasive 2-HG detection correlated with IDH1/IDH2 mutation and with mass-spectrometric D-2-HG in resected tumour	25

Study (first author, year)	Journal	Design	Sample	Technique / index	Principal quantitative finding	Ref.
Bhandari, 2021	Neuroradiology	Systematic review and meta-analysis of diagnostic test accuracy	9 studies; lower-grade glioma n=181, glioblastoma n=77	2-HG MRS for IDH status	Lower-grade glioma: sensitivity 93% (95% CI 58-99), specificity 84% (95% CI 51-96); glioblastoma: 84% (25-99) and 97% (43-100)	26
Xu, 2021	Eur J Radiol	Retrospective head-to-head comparison at 3 T	51 untreated gliomas (13 grade 2, 17 grade 3, 21 grade 4; 25 IDH-mutant)	APTw vs DKI (MD, FA, MK, KFA)	APTw difference discriminated both grade and IDH status; consistently superior to all DKI indices; MD and MK separated grade 4 from grade 2-3 only	24
Wu, 2024	Eur Radiol	Prospective, SVM radiomic modelling with sensitivity analysis	129 adult-type diffuse gliomas	APTw metrics and APTw-derived radiomics	Normalised CESTR AUC 0.88 for IDH; radiomic model accuracy 84% (AUC 0.87) for IDH, 90% (AUC 0.95) glioblastoma vs oligodendroglioma, 63% (AUC 0.63) oligodendroglioma vs astrocytoma	27
Karimian-Jazi, 2025	Invest Radiol	Monocentric prospective trial, 3 T	371 screened; 30 recurrence, 12 pseudoprogression	APTw CEST MRI	APTw 1.99% in progressive disease vs 1.26% in pseudoprogression (p=0.008); enhancing tumour 1.99% vs non-enhancing FLAIR 1.36% (p=0.001)	28
Tsakiris, 2020	World Neurosurg	Systematic review and meta-analysis	24 studies, 900 patients	DWI vs PWI for progression vs pseudoprogression	DWI sensitivity 0.88 / specificity 0.85 (AUC 0.916); PWI 0.85 / 0.79 (AUC 0.907); no significant difference	41
Tian, 2023	BMJ Open	Bayesian network meta-analysis of direct-comparison studies	15 studies (8,853 records screened)	PET tracers and MRI for recurrent glioma	18F-FET ranked highest on SUCRA for sensitivity, specificity, PPV and accuracy, followed by 18F-FDOPA; certainty of evidence moderate	34
Puranik, 2025	Neuroradiology	Retrospective, multidisciplinary-clinic adjudicated reference standard	171 post-treatment grade 3-4 gliomas with equivocal MRI	18F-FET PET, TBR threshold 2.5	Sensitivity 91.6%, specificity 76.9%, diagnostic accuracy 87.1%	33
Muller, 2025	Neuro Oncol	Retrospective comparative study, two independent investigators	125 newly diagnosed IDH-wildtype glioblastoma	PET RANO 1.0 vs MRI-RANO measurable disease	Measurable disease in 90.4% by 18F-FET PET vs 45.6% by MRI (p<0.001); 56/68 (82.4%) MRI-unmeasurable patients were PET-measurable	31

Study (first author, year)	Journal	Design	Sample	Technique / index	Principal quantitative finding	Ref.
Kickingeder, 2019	Lancet Oncol	Multicentre retrospective development and validation	455 training; 40 patients / 239 scans independent testing; EORTC-26101 trial across 38 institutions	Artificial neural network volumetric segmentation	Automated time to progression more reliable than RANO assessment and at least equivalent as a surrogate endpoint for overall survival	49
van der Voort, 2023	Neuro Oncol	Multicentre multi-task deep learning with independent external test set	1,508 patients (16 institutes) training; 240 patients (13 institutes) testing	Single 3D CNN for IDH, 1p/19q, grade and segmentation	IDH AUC 0.90; 1p/19q AUC 0.85; grade AUC 0.81; mean whole-tumour Dice 0.84	50
Jian, 2021	Neurosurgery	Systematic review and meta-analysis (PRISMA, QUADAS-2)	44 original articles	Machine learning on preoperative MRI	IDH: pooled sensitivity 0.88 (0.83-0.91) and specificity 0.86 (0.79-0.91) in training, 0.83-0.85 in validation; MGMT and 1p/19q 0.76-0.83	51
Chen, 2024	Front Oncol	Systematic review and meta-analysis (METHodological Radiomics Score, QUADAS-2)	14 studies, 1,740 patients	ML-based MR radiomics for IDH	Pooled AUC 0.90 (0.87-0.92); sensitivity 0.83 (0.71-0.90); specificity 0.84 (0.74-0.90); diagnostic odds ratio 25	52
Jayachandran Preetha, 2021	Lancet Digit Health	Multicentre retrospective cohort, independent trial test set	775 institutional + CORE (260) + CENTRIC (505) for development; EORTC-26101 (528 patients, 1,924 examinations) for testing	Deep-learning synthesis of post-contrast T1-weighted MRI	Median SSIM 0.818; time to progression 4.2 vs 4.3 months for synthetic vs true post-contrast (p=0.33); comparable prognostic strength	54
Mellinghoff, 2023	N Engl J Med	Randomised, double-blind phase 3 trial (INDIGO) with imaging-based primary endpoint	331 patients with residual or recurrent grade 2 IDH-mutant glioma	Blinded independent review of imaging-based progression-free survival	Median PFS 27.7 vs 11.1 months (HR 0.39, 95% CI 0.27-0.56, p<0.001); time to next intervention IHR 0.26 (0.15-0.43)	48

ADC, apparent diffusion coefficient; APTw, amide proton transfer-weighted; AUC, area under the receiver operating characteristic curve; CE:STR, chemical exchange saturation transfer ratio; CI, confidence interval; CNN, convolutional neural network; DKI, diffusion kurtosis imaging; DSC, dynamic susceptibility contrast; DWI, diffusion-weighted imaging; FA, fractional anisotropy; HR, hazard ratio; HSROC, hierarchical summary receiver operating characteristic; IDH, isocitrate dehydrogenase; KFA, kurtosis fractional anisotropy; MD, mean diffusivity; MGMT, O6-methylguanine-DNA methyltransferase; MK, mean kurtosis; MRS, magnetic resonance spectroscopy; NPV, negative predictive value; PET, positron emission tomography; PFS, progression-free survival; PPV, positive predictive value; PSR, percentage signal recovery; PWT, perfusion-weighted imaging; RANO, Response Assessment in Neuro-Oncology; rCBV, relative cerebral blood volume; SSIM, structural similarity index measure; SUCRA, surface under the cumulative ranking curve; SVM, support vector machine; TBR, tumour-to-background ratio; TCGA/TCLA, The Cancer Genome Atlas / The Cancer Imaging Archive.

Scope and literature search

PubMed was searched for English-language articles indexed up to September 2026. Search strings combined terms for the disease (diffuse glioma, astrocytoma, oligodendroglioma, glioblastoma), the taxonomy (WHO 2021 classification, IDH, 1p/19q, MGMT, CDKN2A/B, H3 K27), individual techniques (diffusion-weighted imaging, diffusion tensor and kurtosis imaging, dynamic susceptibility contrast, dynamic contrast-enhanced, arterial spin labelling, magnetic resonance spectroscopy, 2-hydroxyglutarate, chemical exchange saturation transfer, amide proton transfer, amino acid PET, synthetic MRI), response assessment (RANO, mRANO, iRANO, RANO 2.0, PET RANO, pseudoprogression, radiation necrosis, pseudoresponse) and computation (radiomics, machine learning, deep learning, convolutional neural network).

Because this is a narrative and not a systematic review, article selection was purposive. Preference was given, in descending order, to consensus statements and practice guidelines from the Response Assessment in Neuro-Oncology (RANO) group and allied societies; diagnostic test-accuracy meta-analyses; multicentre or externally validated primary studies; and randomised trials in which imaging constituted the primary endpoint. Single-centre exploratory studies were retained only where they document a technique for which higher-level evidence does not yet exist. No formal risk-of-bias appraisal was performed, and the reader

should treat the effect estimates reproduced in Table 2 as descriptive rather than pooled.

What changed in 2021, and why it matters at the workstation

The 2021 classification introduced four operational changes with direct radiological consequences^[1]. First, grading is now performed within tumour type rather than across the diffuse glioma family, and Arabic numerals replaced Roman ones. Second, molecular criteria may assign grade independently of histology: homozygous deletion of CDKN2A/B upgrades an IDH-mutant astrocytoma to CNS WHO grade 4 even in the absence of necrosis or microvascular proliferation, and an IDH-wildtype diffuse astrocytic tumour in an adult that harbours TERT promoter mutation, EGFR amplification or combined gain of chromosome 7 and loss of chromosome 10 is classified as glioblastoma even when it looks histologically lower-grade. Third, oligodendroglioma requires the conjunction of IDH mutation and 1p/19q codeletion, so the previously common category of mixed oligoastrocytoma effectively disappears. Fourth, paediatric-type diffuse gliomas were separated from adult-type tumours, and midline lesions defined by H3 K27 alteration constitute their own group, within which further clinico-radiological subtypes continue to be delineated^[1,36].

Two implications deserve emphasis. The first is that a histologically or radiologically “low-grade” appearance can coexist with a grade

4 diagnosis, which invalidates the older habit of inferring aggressiveness from enhancement alone^[3,4]. The second is that imaging has become a triage and stratification instrument rather than a diagnostic substitute: it can indicate which molecular class is likely, guide the biopsy trajectory towards the most representative compartment, and monitor a lesion whose genotype is already known, but it cannot be asked to replace sequencing or methylation profiling^[5].

Standardised acquisition as the rate-limiting step

Every quantitative claim in this field is conditioned by acquisition. The consensus Brain Tumor Imaging Protocol (BTIP), developed in a joint meeting of regulators, imaging scientists, cooperative groups and industry, specified a minimum set of sequences — three-dimensional isotropic T1-weighted images before and after gadolinium, T2- and FLAIR-weighted images, and diffusion-weighted imaging — with defined field strength, slice thickness and contrast timing, precisely to make tumour measurements comparable across sites and time points^[7]. An analogous protocol was subsequently issued for brain metastases^[8], and practical guidance now exists for integrating these protocols into routine departmental workflows, including “minimum” variants for centres that cannot meet every ideal requirement^[9].

Perfusion imaging received its own consensus. The dynamic susceptibility contrast (DSC) protocol endorsed by the DSC-MRI Standardization Subcommittee of the Jumpstarting Brain Tumor Drug Development Coalition harmonised field strength, echo time, flip angle, contrast preload and leakage-correction strategy, and was deliberately made compatible with BTIP so that a single examination can serve both structural and haemodynamic purposes^[20]. The importance of these documents is easy to underestimate: the disappointing reproducibility of relative cerebral blood volume (rCBV) thresholds in the older literature is largely attributable to protocol heterogeneity rather than to any failure of the underlying physiology^[19,20]. Standardisation is therefore not a bureaucratic preliminary to biomarker research; it is the substance of it.

Structural MRI signs with molecular value

The best-characterised structural radiogenomic marker is the T2-FLAIR mismatch sign: a lesion that is homogeneously hyperintense on T2-weighted images but relatively hypointense on FLAIR except for a hyperintense peripheral rim. In the original TCGA/TCIA analysis of 125 lower-grade gliomas read by two independent neuroradiologists, all 15 positive cases were IDH-mutant and 1p/19q non-codeleted, giving a positive predictive value of 100% with a negative predictive value of 54%; a separate institutional cohort of 82 patients reproduced the finding,

with substantial interreader agreement in both cohorts^[10]. A three-database validation study of 154 genotyped lower-grade gliomas confirmed substantial agreement for the sign (kappa 0.75) and reported sensitivity 51%, specificity 100%, positive predictive value 100% and negative predictive value 68%^[11].

Two diagnostic meta-analyses have since quantified this asymmetry. Pooling 12 studies and 1,053 patients, the sign showed sensitivity 42% (95% CI 28-58) and specificity 100% (95% CI 88-100), with an area under the hierarchical summary receiver operating characteristic curve of 0.77 and heterogeneity largely explained by a threshold effect^[12]; an independent meta-analysis reached concordant conclusions^[13]. The practical reading is that a positive sign is close to diagnostic, whereas a negative sign is uninformative.

Reports of false positives have accumulated, and they are instructive rather than disqualifying. Most reflect variable application of the imaging criteria, differences in acquisition, or inclusion of lesions outside the intended population, and dysembryoplastic neuroepithelial tumours in particular can display the sign^[14,16]. Histopathological correlation suggests that the mismatch reflects a microcystic, low-cellularity matrix with a denser peripheral rim^[15]. Refinements have accordingly been proposed: requiring a hyperintense FLAIR rim and combining the sign with other radiological features improves identification of the IDH-mutant 1p/19q non-codeleted subtype^[17], and the sign correlates with

11C-methionine uptake in lower-grade diffuse gliomas, suggesting a metabolic counterpart^[35]. Quantification helps as well. In a comparison of four radiologists, a three-dimensional convolutional neural network and synthetic MRI relaxometry in 33 IDH-mutant gliomas, mean sensitivity and specificity were 76.3% and 100% for the readers versus 94.7% and 92.9% for the network, and a combined T1/T2 relaxation-time threshold reached 94.4% sensitivity and 100% specificity with an area under the curve of 0.981^[18]. Small as that cohort is, it illustrates a general direction of travel: converting a categorical visual sign into a continuous, objective measurement raises sensitivity without sacrificing specificity.

Advanced imaging techniques

Table 1 summarises the techniques discussed below. The organising principle is that each interrogates a distinct biological property — cellularity, vascularity, metabolism, protein content, amino acid transport — and that their errors are therefore partly independent, which is the argument for multiparametric rather than sequential use.

Diffusion-weighted, tensor and kurtosis imaging

Apparent diffusion coefficient (ADC) values are inversely related to cellular density and, at the group level, are lower in IDH-wildtype than IDH-mutant high-grade gliomas; in a series of 58 histologically proven high-grade gliomas, this difference was statistically significant but with

substantial overlap between groups, so ADC alone was insufficient for individual classification^[21]. Diffusion tensor imaging (DTI) adds directional information; histogram analysis of DTI metrics and functional diffusion maps detected structural change in 21 low-grade gliomas receiving dose-dense temozolomide before conventional volumetric change was apparent, illustrating the potential of diffusion metrics as early response markers in slowly evolving tumours^[23]. Diffusion kurtosis imaging (DKI) models non-Gaussian diffusion and yields mean kurtosis, which differentiated grade 4 from grade 2-3 tumours in a 51-patient cohort, although it did not separate grade 2 from grade 3 and was outperformed for both grading and IDH prediction by amide proton transfer imaging in the same patients^[24].

Perfusion imaging: DSC, DCE and arterial spin labelling

Perfusion MRI is the most widely deployed advanced technique in neuro-oncology and, paradoxically, the one whose evidence base is most sobering. A Cochrane review of MR perfusion for distinguishing solid non-enhancing low-grade from high-grade gliomas at first presentation identified only seven studies with 115 evaluable participants; using the conventional rCBV threshold of 1.75, summary sensitivity was 0.83 (95% CI 0.66-0.93) and specificity 0.48 (95% CI 0.09-0.90), and the authors concluded that available evidence precluded reliable estimation of performance^[19].

This is a statement about the literature, not about physiology: the included studies used heterogeneous acquisition and post-processing, and the reference standard antedated molecular classification. The DSC consensus protocol was written to address exactly this problem^[20].

Where DSC does add value is in parameters beyond rCBV. In the 58-patient high-grade glioma series cited above, percentage signal recovery — a marker of contrast leakage and vessel permeability — discriminated IDH status with an area under the curve of 0.938 and 87% accuracy, and combining percentage signal recovery with rCBV raised the area under the curve to 0.955, outperforming ADC^[21]. Dynamic contrast-enhanced (DCE) MRI provides pharmacokinetic permeability estimates such as K_{trans}, but was represented by a single study in the Cochrane analysis, precluding quantitative synthesis^[19]. Arterial spin labelling (ASL) offers contrast-free quantification of cerebral blood flow, which is attractive in patients undergoing frequent surveillance or with impaired renal function, and has documented applications in tumour grading, surveillance and the recognition of treatment complications, including radiation necrosis^[22].

Magnetic resonance spectroscopy and 2-hydroxyglutarate

IDH1 and IDH2 mutations produce the oncometabolite D-2-hydroxyglutarate (2-HG), which accumulates in tumour tissue and resonates at approximately 2.25 ppm. Choi and colleagues developed an optimised proton

spectroscopy sequence and estimated 2-HG concentrations in 30 patients, with detection correlating both with IDH1/IDH2 mutation and with mass-spectrometric measurement of D-2-HG in resected tissue^[25]. This remains one of the few genuinely direct molecular readouts available to MRI.

Diagnostic performance in aggregate is promising but imprecise. A test-accuracy meta-analysis of nine studies reported pooled sensitivity 93% (95% CI 58-99) and specificity 84% (95% CI 51-96) for lower-grade gliomas (n=181), and sensitivity 84% (95% CI 25-99) with specificity 97% (95% CI 43-100) for glioblastoma (n=77) [26]. The confidence intervals convey the essential limitation: sample sizes are small, the number of IDH-mutant glioblastomas studied is very small, and hierarchical summary curves showed poor predictive accuracy. 2-HG spectroscopy also demands technical conditions — adequate voxel size, high field strength, careful spectral fitting — that restrict it to specialised centres. Its most plausible near-term role is longitudinal, as a pharmacodynamic marker in patients treated with mutant IDH inhibitors.

Chemical exchange saturation transfer and amide proton transfer

Amide proton transfer-weighted (APT_w) imaging, a chemical exchange saturation transfer technique, generates contrast from mobile amide protons of cytosolic proteins and peptides and thus reports on protein content and pH. In a

prospective study of 129 patients with adult-type diffuse gliomas, APT_w metrics were significantly higher in glioblastoma than in astrocytoma or oligodendroglioma and higher in IDH-wildtype and high-grade tumours, with an area under the curve of 0.88 for the normalised chemical exchange saturation transfer ratio; radiomic models built on APT_w maps achieved 84% accuracy (AUC 0.87) for IDH status and 90% accuracy (AUC 0.95) for separating glioblastoma from oligodendroglioma, but performed poorly in distinguishing oligodendroglioma from astrocytoma (63% accuracy)^[27]. In a head-to-head comparison with DKI in 51 patients, APT_w was superior for both grading and IDH prediction^[24].

APT_w is also being evaluated in the post-treatment setting. In a monocentric prospective trial that screened 371 patients under surveillance and analysed 30 with recurrence and 12 with pseudoprogression, APT_w signal was higher in progressive disease than in pseudoprogression (1.99% versus 1.26%, p=0.008), and revealed heterogeneity within the FLAIR abnormality that conventional sequences did not show [28]. Sample sizes remain small and thresholds are not yet transferable between vendors, but the technique has the advantage of requiring no contrast agent and no radiotracer.

Amino acid PET

Radiolabelled amino acid tracers — principally ¹⁸F-FET, ¹¹C-methionine and ¹⁸F-FDOPA — exploit upregulated L-type

amino acid transport and produce tumour-to-background contrast that is largely independent of blood-brain barrier disruption. Joint EANM/EANO/RANO practice guidelines and SNMMI procedure standards codified acquisition, analysis and reporting for these tracers and for 18F-FDG in glioma^[29].

The clearest clinical gain is in the post-treatment setting. In a Bayesian network meta-analysis of 15 direct-comparison studies, 18F-FET ranked highest for sensitivity, specificity, positive predictive value and accuracy in differentiating glioma recurrence from post-radiotherapy change, followed by 18F-FDOPA, with moderate certainty of evidence^[34]. In a single-centre study of 171 patients with post-treatment grade 3-4 glioma and equivocal MRI, a tumour-to-background ratio threshold of 2.5 yielded sensitivity 91.6%, specificity 76.9% and diagnostic accuracy 87.1% against histopathology or adjudicated multidisciplinary follow-up^[33]. A further series of 45 patients found that 18F-FET parameters carried prognostic as well as diagnostic information, predicting progression-free and overall survival^[32].

A second contribution is to the definition of measurable disease. Comparing PET RANO 1.0 with MRI-based RANO in 125 patients with newly diagnosed IDH-wildtype glioblastoma imaged after resection or biopsy and before radiotherapy, 90.4% had measurable disease on 18F-FET PET versus 45.6% on MRI ($p < 0.001$); of 68 patients without measurable disease on MRI,

56 (82.4%) had measurable disease on PET, while no patient measurable on MRI was unmeasurable on PET [31]. Since trial eligibility and response calculation both depend on the presence of measurable disease at baseline, this discrepancy has direct methodological consequences. The main constraints on amino acid PET remain tracer availability, cost and the limited number of centres with on-site production.

Quantitative and synthetic MRI

Synthetic MRI derives T1 and T2 relaxation times and proton density from a single acquisition and can generate contrast-weighted images retrospectively. Its interest here is the substitution of an operator-dependent visual judgement by a number: in the 33-patient comparison described above, a combined threshold on T1 and T2 relaxation times separated astrocytoma from oligodendroglioma with an area under the curve of 0.981, exceeding both radiologists and a convolutional neural network applied to the T2-FLAIR mismatch sign^[18]. Quantitative relaxometry, radiomics and deep learning are converging on the same objective, which is to make the same lesion yield the same number in different hands and on different scanners.

Radiogenomics: what imaging can and cannot infer

IDH status is the marker most accessible to imaging, through the T2-FLAIR mismatch

sign^[10-13,17,18], ADC and perfusion parameters^[21], 2-HG spectroscopy^[25,26], APTw^[24,27] and machine learning applied to conventional sequences^[50,51,52]. Reported performance clusters around an area under the curve of 0.85-0.90 in validated settings, which is useful for stratification but short of the accuracy required to forgo tissue diagnosis.

1p/19q codeletion is harder. It is inferred largely by exclusion — a non-mismatch, calcified, indistinctly margined frontal lesion in an IDH-mutant tumour — and dedicated models reach areas under the curve around 0.85 in independent test sets^[50], with pooled sensitivity and specificity of 0.76-0.83 in meta-analysis^[51]. Distinguishing oligodendroglioma from astrocytoma is precisely the task at which several advanced techniques fail: APTw radiomics achieved only 63% accuracy for this contrast, despite performing well elsewhere^[27].

MGMT promoter methylation is the most contested. Radiomic and machine-learning models continue to report encouraging figures — pooled sensitivity and specificity between 0.76 and 0.83 in training datasets^[51], and improved performance with genetic-algorithm feature optimisation in single-centre work^[53] — but the biological plausibility of a robust imaging signature for a promoter methylation state is weaker than for IDH, and reproducibility across cohorts has been inconsistent. Claims in this area warrant particular scepticism until multicentre external validation is available.

CDKN2A/B homozygous deletion, now a grading criterion in IDH-mutant astrocytoma^[1],

has no established imaging surrogate and represents an obvious research target. In midline tumours, H3 K27 alteration defines a distinct entity whose emerging subtypes have recognisable radiological features: tumours co-altered in H3 K27 and BRAF or FGFR1 show atypical calcification and a solid component, arise preferentially in the thalamus and have longer overall survival than other diffuse midline gliomas^[36].

Presurgical planning and the quantification of resection

Task-based and resting-state functional MRI and diffusion tractography are now routine in the presurgical assessment of gliomas in or near eloquent cortex and white matter, with good concordance against intraoperative stimulation mapping and an established role in planning the resection corridor^[37]. Their limitations are well known — neurovascular uncoupling in highly vascular tumours, susceptibility artefact after prior surgery, and the dependence of tractography on the reconstruction algorithm — and they are best read as complementary to, not a replacement for, intraoperative mapping.

The RANO resect group has since reframed the imaging task around quantification. Its review of the oncological role of resection in newly diagnosed adult-type glioma defined by the WHO 2021 classification concluded that the survival benefit of more extensive resection unfolds over months to decades depending on molecular profile, that supramaximal resection

may confer additional benefit in tumours with aggressive natural history, and — of most direct relevance to radiology — that neuro-oncological trials have frequently failed to quantify the extent of resection at all^[38]. Volumetric measurement of residual contrast-enhancing and non-enhancing tumour, rather than a qualitative statement of gross-total or subtotal resection, is therefore a concrete deliverable that neuroradiology can supply. Amino acid PET may extend this quantification to tumour that conventional sequences do not display^[31].

The post-treatment brain: pseudoprogression, radiation necrosis and pseudoresponse

Three distinct phenomena confound post-treatment interpretation. Pseudoprogression is a transient increase in contrast enhancement occurring in roughly 20-30% of patients with glioblastoma within the first months after chemoradiotherapy, driven by treatment-induced inflammation and blood-brain barrier disruption rather than tumour growth^[43]. Radiation necrosis is a later, often progressive process with overlapping imaging features. Pseudoresponse is the inverse error: antiangiogenic agents reduce vascular permeability and hence contrast enhancement within days, without a corresponding antitumour effect, while non-enhancing tumour may continue to expand on T2/FLAIR^[43,39].

Advanced imaging helps but does not resolve these problems. A meta-analysis of

24 studies and 900 patients found diffusion-weighted imaging and perfusion-weighted imaging comparably accurate in distinguishing true progression from pseudoprogression in glioblastoma — sensitivity 0.88 and specificity 0.85 for DWI versus 0.85 and 0.79 for PWI, with areas under the curve of 0.916 and 0.907 respectively and no significant difference between them^[41]. Amino acid PET performs better in this specific setting^[33,34], and APTw CEST shows early promise^[28]. Immunotherapy adds a further layer: pseudoprogression may be delayed, and imaging changes may reflect intratumoural immune infiltration^[40]. In practice, no single modality is decisive, and multidisciplinary adjudication with short-interval follow-up remains the reference standard in most centres — which is precisely the design used in the largest FET PET series^[33].

Response assessment: from Macdonald to RANO 2.0 and PET RANO 1.0

Formal response assessment in neuro-oncology began with the Macdonald criteria, which defined four response categories based on bidimensional measurement of contrast enhancement on CT or MRI, interpreted alongside corticosteroid dose and neurological status^[42]. The RANO criteria of 2010 retained the bidimensional approach but incorporated non-enhancing disease, addressed pseudoprogression by requiring confirmation within the first 12 weeks after radiotherapy, and acknowledged pseudoresponse under antiangiogenic therapy^[43].

Immunotherapy-specific modifications (iRANO) extended the window for confirming progression to account for delayed responses and therapy-induced inflammation^[44].

The proliferation of variants — RANO for high-grade and low-grade gliomas, modified RANO, iRANO — became itself a source of inconsistency, and RANO 2.0 was developed to unify them. Informed by patient-level data from studies comparing the criteria, RANO 2.0 applies a single framework to high- and low-grade gliomas in adults; uses the post-radiation rather than the pre-radiation MRI as baseline in newly diagnosed glioblastoma, since that scan proved superior; specifies when confirmation scans are and are not required; and permits volumetric measurement as an alternative to bidimensional assessment^[45,46]. Practical guidance for neuroradiologists on operationalising these rules has been published^[47].

PET RANO 1.0 provides the first structured framework for amino acid PET in diffuse gliomas as defined by the 2021 classification, specifying baseline and follow-up timepoints and response categories, explicitly as a conceptual scaffold intended to encourage prospective validation rather than as a finished standard^[30]. Its first comparative application already exposed a substantive discrepancy in what counts as measurable disease^[31].

The therapeutic context has also changed what imaging endpoints must capture. In the phase 3 INDIGO trial, 331 patients with residual

or recurrent grade 2 IDH-mutant glioma were randomised to vorasidenib or placebo, with imaging-based progression-free survival by blinded independent review as the primary endpoint; median progression-free survival was 27.7 versus 11.1 months (hazard ratio 0.39, 95% CI 0.27-0.56, $p<0.001$)^[48]. When the treated population consists of largely non-enhancing, slowly growing tumours and the endpoint is imaging-defined progression over years, the reproducibility of FLAIR volumetry and the definition of growth rate become the determinants of trial validity — a role neuroradiology did not previously occupy.

Artificial intelligence and radiomics

AI has advanced furthest where the task is measurement rather than inference. An artificial neural network trained on 455 single-institution examinations and tested in an independent longitudinal cohort and in the multicentre EORTC-26101 trial (38 European institutions) performed fully automated volumetric segmentation of contrast-enhancing tumour and non-enhancing T2 abnormality, and the resulting automated time to progression was more reliable than RANO assessment while performing at least as well as a surrogate endpoint for overall survival^[49]. This is the clearest existing demonstration that automation can improve, not merely accelerate, a task that clinicians already perform.

Molecular prediction has also reached credible multicentre performance. A single multi-task convolutional neural network trained on

1,508 patients from 16 institutions and tested on 240 patients from 13 other institutions predicted IDH mutation (AUC 0.90), 1p/19q codeletion (AUC 0.85) and grade (AUC 0.81) while simultaneously segmenting the tumour with a mean whole-tumour Dice coefficient of 0.84^[50]. Meta-analyses are consistent with this order of magnitude: across 44 studies, pooled sensitivity and specificity for IDH prediction were 0.88 and 0.86 in training and 0.83-0.85 in validation sets, with MGMT methylation and 1p/19q codeletion in the 0.76-0.83 range^[51]; a later meta-analysis of 14 studies and 1,740 patients reported an area under the curve of 0.90 with pooled sensitivity 0.83 and specificity 0.84 for IDH^[52].

A third and less obvious application is the reduction of acquisition burden. Deep networks can synthesise post-contrast T1-weighted images from pre-contrast sequences with a structural similarity index of 0.818 in independent trial data, and volumetric response assessment derived from synthetic images yielded a median time to progression of 4.2 versus 4.3 months against true post-contrast images ($p=0.33$), with comparable prognostic strength^[54]. Deep-learning reconstruction of undersampled k-space, validated across four multicentre cohorts, preserved image quality and oncological biomarkers at substantial acceleration factors^[55]. If these results are confirmed prospectively, the implication is fewer gadolinium administrations and shorter examinations in a population that undergoes lifelong surveillance.

The obstacles are equally clear. Most models are trained on retrospective, single-vendor data; external validation is the exception rather than the rule; radiomic features are sensitive to acquisition parameters, segmentation variability and normalisation choices; and reporting quality, as assessed by instruments such as the Radiomics Quality Score and QUADAS-2, is frequently poor^[51,52]. Meta-analytic pooling in this domain therefore aggregates heterogeneity as much as signal. The credible near-term contribution of AI in neuro-oncological imaging is automated segmentation and volumetry embedded in a standardised protocol, with molecular prediction remaining a stratification aid.

Limitations of the current evidence and a research agenda

Four structural weaknesses recur across the literature reviewed here. First, reference standards have shifted: much of the perfusion and diffusion literature was generated under the 2007 or 2016 classifications, so its “high-grade” and “low-grade” categories do not map cleanly onto WHO 2021 entities, and re-analysis of legacy cohorts against molecular endpoints is needed^[1,19]. Second, sample sizes for the most mechanistically interesting techniques — 2-HG spectroscopy, CEST, quantitative relaxometry — remain small, and confidence intervals correspondingly wide^[26,27,28]. Third, protocol heterogeneity persists despite consensus documents, and adherence to BTIP and the DSC protocol is not routinely reported

in primary studies^[7,9,20]. Fourth, publication and threshold-selection bias inflate diagnostic accuracy estimates, most visibly in radiomics^[51,52].

A pragmatic agenda follows. Prospective multicentre validation of PET RANO 1.0 and of volumetric RANO 2.0 in the same cohorts would clarify how much of the apparent gain from PET reflects genuine biology rather than differing definitions of measurable disease^[30,31,46]. Imaging correlates of CDKN2A/B deletion and of the newer H3 K27-altered subtypes are unexplored^[11,36]. Head-to-head comparison of contrast-free techniques — ASL, APTw, synthetic MRI, deep-learning-synthesised enhancement — against gadolinium-based reference standards addresses a concrete clinical need in patients under long-term surveillance^[22,27,54]. Finally, adherence to standardised protocols and transparent reporting of external validation should be treated as inclusion criteria rather than desiderata in future syntheses.

CONCLUSION

Neuroradiology has not become a substitute for molecular pathology in diffuse glioma, and the evidence reviewed here suggests it will not. What it has become is something arguably more useful: the instrument through which molecular categories are translated into decisions over time. The T2-FLAIR mismatch sign shows how a simple, near-specific structural finding can enter clinical reasoning

without any claim to sensitivity; amino acid PET shows how a modality can outperform MRI in a narrowly defined but high-stakes question; RANO 2.0 and PET RANO 1.0 show how measurement conventions determine what a trial can conclude; and automated segmentation shows how a machine can be more reliable than an expert at a task the expert never wanted. The unifying requirement across all of these is standardisation of acquisition and analysis, which remains the most consequential and least glamorous priority in the field.

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1) The authors declare that there are no conflicts of interest of any kind.

2) The authors declare, if applicable, that they agree with the policies for the ethical use of Artificial Intelligence, reporting this in the acknowledgments or methods section of the article, in accordance with the guidelines of WAME (World Association of Medical Editors).



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